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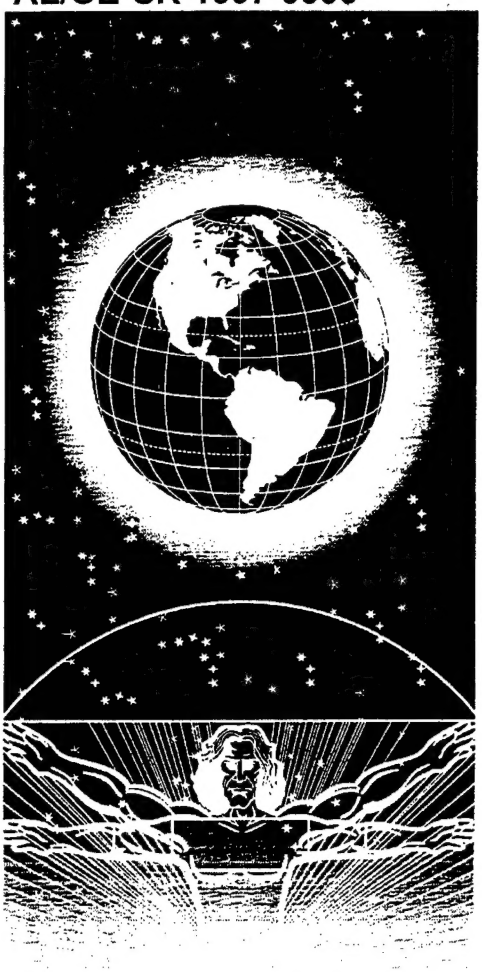

UNITED STATES AIR FORCE
ARMSTRONG LABORATORY

TCE FLAGSHIP TECHNICAL PAPER: DATA FOR VALIDATION OF HUMAN PBPK MODEL

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September 1997

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This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

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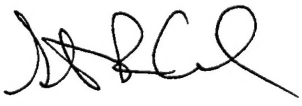

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The Armstrong Laboratory Occupational and Environmental Health Directorate, Toxicology Division is supporting the current flagship review of the environmental risks of trichloroethylene (TCE) being conducted by the U.S. Environmental Protection Agency (EPA). Operational Technologies assisted with the following objectives: 1) gathering physiologically-based pharmacokinetic (PBPK) data from published human studies which used TCE or its known metabolites as the dosing agent, 2) compiling physiological parameters (i.e., organ weight, blood volume, percent body fat and body weight) used in PBPK models, 3) calculating time weighted averages (TWAs) of 17 volunteer subjects exposed to TCE at Research Triangle Park (RTP) and 4) summarizing available human and animal toxicological studies on dichloroacetic acid (DCA). The main purpose of these tasks was to assist in refining TCE PBPK modeling efforts performed at the Toxicology Division by providing human data which may be used for statistical analysis and/or verification of PBPK modeling work.

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LIST OF ABBREVIATIONS

μCi	micro-Curie
μg	microgram
CH	chloral hydrate
CO_2	carbon dioxide
DCA	dichloroacetic acid
DCAC	dichloroacetate
dy	day
EPA	Environmental Protection Agency
g	gram
GC	gas chromatograph
hr	hour
IARC	International Agency for Research on Cancer
iv	intravenous
kg	kilogram
K_m	dissociation constant
L	liter
LD_{50}	lethal dose for 50% of study animals
LDH	lactate dehydrogenase
mg	milligram
min	minute
mL	milliliter
mL	milliliter
mmol	millimole
mol	mole
n	number of study subjects
NA	not applicable
PBPK	physiologically-based pharmacokinetic
ppm	parts per million
RBC	red blood cell
RTP	Research Triangle Park
sec	second
$t_{1/2}$	half life
TCA	trichloroacetic acid
TCAC	trichloroacetate
TCE	trichloroethylene
TCOH	trichloroethanol
TWA	time weighted average
V_{max}	maximum velocity
yr	year

PREFACE

This effort was performed by Operational Technologies Corporation, 1010 Woodman Drive, Suite 160, Dayton OH 45432 under the Project Management of Mr. Erik Vermulen. The work was completed under U.S. Air Force Contract F41624-94-D-9003 between April 1996 and February 1997. Lt Col Terry Childress, Director of Armstrong Laboratory Occupational and Environmental Health Directorate Toxicology Division, served as contract monitor.

Operational Technologies Corporation (OpTech) would like to extend special thanks to the Principal Investigator of this effort, Dr. Jeffrey W. Fisher, for his instruction and guidance in this effort.

TCE FLAGSHIP TECHNICAL PAPER: DATA FOR VALIDATION OF HUMAN PBPK MODEL

INTRODUCTION

A flagship review of the environmental risks of trichloroethylene (TCE) is currently being conducted by the U.S. Environmental Protection Agency (EPA). The Armstrong Laboratory Occupational and Environmental Health Directorate, Toxicology Division is supporting this review. The work completed by Operational Technologies on the TCE Flagship review was divided into the following objectives: 1) gather physiologically-based pharmacokinetic (PBPK) data from published human studies which used TCE or its known metabolites as the dosing agent, 2) compile physiological parameters (i.e., organ weight, blood volume, percent body fat and body weight) used in PBPK models, 3) calculate time weighted averages (TWAs) of 17 volunteer subjects exposed to TCE at Research Triangle Park (RTP) and 4) summarize available human and animal toxicological studies on dichloroacetic acid (DCA). The main purpose of these tasks was to assist in refining TCE PBPK modeling efforts performed at the Toxicology Division by providing human data which may be used for statistical analysis and/or verification of PBPK modeling work. OpTech was not requested to perform analysis on the data collected, however considerable evaluation of the data was performed in order to find data best suited for PBPK modeling.

In addition, OpTech was requested to summarize select human and animal studies, including review articles, and provide background information on human pharmacokinetics, toxicity, carcinogenicity and teratogenicity of DCA. Dichloroacetic acid is not only a major metabolite of TCE, but both chloroform and DCA are byproducts of water chlorination. This information was used by the Principle Investigator (PI), who serves on the steering committee to evaluate chloroform and dichloroacetic acid as case studies for application of EPA's proposed guidelines for carcinogen risk assessment.

LITERATURE SEARCHES FOR TCE METABOLITES DATA

Comprehensive literature searches were performed on TCE and its known metabolites: trichloroacetic acid (TCA), DCA, choral hydrate (CH) and trichloroethanol (TCOH). The objective of searching for studies in which the metabolites were the dosing agents was to obtain additional PBPK data that may not be reflected in existing TCE models. Searches were performed in available National Library of Medicine's Medline databases from 1966 through 1995 and Toxline databases from 1990 through 1995. Dialog's Occupational Safety and Health database (based on National Institute of Occupational Safety and Health's NIOSHTIC) was also accessed to some extent as available.

Study articles were retrieved from the Wright-Patterson Air Force Base toxicology, medical and technical libraries as well as from Wright State University and University of Cincinnati libraries. Table 1 presents a brief summary of topics searched during this effort.

Table 1
Summary of Literature Searches for Pharmacokinetic Data on TCE

	Databases Accessed	Biologic* and Monitor*	Blood or Urine (Human)	Dichlorovinylcysteine	Exhal*	Expos* and Human	Glutathione	GSH	Human	Lyase	Metabol* (Human)	PB-PK or PBPK	Pharmacokinetic*
Trichloroethylene (79-01-6)	a b c	a c	a c	a	a	a 1	a	a		a	a c	b	a c
Chloral/Chloral Hydrate (75-87-6/302-17-0)	a b c	b c	a c	b	a	a c	b	b	a c	b	a c	b	a c
Dichloroacetic/Dichloroacetate (79-43-6/13425-80-4)	a b	b	a	b	b	a	b	b	a	b	a	b	a
Trichloroethanol (115-20-8)	a b	a	a	b		a	b	b	b	b	a	b	a
Dekant-W	a												
PB-PK or PBPK	b								b				
Stacpoole	a												

a Medline 1966-95 Toxline 1990-95
b Medline 1966-82, 1990-95 Toxline 1990-95
c Occupational Safety & Health on Dialog
1 Refined with Occupat*, then with Volunt*

METHOD FOR EXTRACTION OF PUBLISHED TCE METABOLITES DATA

The actual process of extracting relevant data from kinetic studies was labor intensive. Once the selected studies were retrieved from area libraries, each was evaluated as to the usefulness of its data. Human TCE and TCE-metabolite dosing studies were considered useful only if the dose was defined and measurements of metabolites were identifiable with respect to time from the initial dose. Additionally, total urine collected over time was necessary; urine sampling at given intervals was not acceptable. Also, the analytical method for TCOH in blood and urine had to be defined. The analytical method is relevant because it determines whether the measured TCOH represents free TCOH or a total TCOH complex with glucuronide. Consultation with the PI occurred as needed to delineate any questionable data extrapolation procedures. All references used within the studies were scanned to identify other potential sources of measured human metabolite data.

Research on TCE and metabolites in human subjects is limited. Of the literature evaluated, only 24 studies satisfied the criteria above. These studies were conducted primarily during and prior to the 1970s.

Data from useful studies were entered into spreadsheets. Concentrations vs. time data available only in charts and graphs were digitized into a coordinate system using EASYDIJ© (Version 8.0) and entered into spreadsheets. All continuous variables were entered so that measured concentrations and time of measurement from the initial dose corresponded. This format readily allows for statistical analysis of the published data. Categorical variables such as sex, age and weight were also entered into the spreadsheets to correspond with individual metabolite data.

For the purpose of making the data comparable from one study to another, all measured variables were converted to common units (e.g., time from initial dose in hours, doses in mg/kg and plasma concentrations in mg/L). Time data within the human studies were normalized to hours from the initial dose or start of the exposure. Measured urinary metabolites were calculated as cumulative excretion over time. The completed spreadsheets of human TCE metabolite data are presented in Attachments I through V.

The final databases (spreadsheets) were quality control checked against the original studies. Approximately 60% of all data taken from graphs and tables were checked against the spreadsheets for accuracy.

CALCULATION OF EXPOSURE LEVEL OF HUMAN VOLUNTEERS AT RESEARCH TRIANGLE PARK

TWAs were calculated for 17 human volunteers exposed to TCE under controlled environmental conditions at Research Triangle Institute, Research Triangle Park (RTP), North Carolina (Kizakevich, 1996). These TWAs are actual exposure levels that will be used to develop the PBPK model (see Table 2), whereas human data gathered previously from existing, published studies will be used for validation purposes. Each subject was exposed to approximately 50 or 100 ppm TCE over a period of 4 hours. Subject numbers beginning with 100 were male participants and those beginning with 200 were females.

Table 2
Summary of TCE TWAs Before and During Exposure
Research Triangle Park, 1995

Subject #	Time in booth before removing masks (hr:min:sec)	TWA before exposure (ppm)	Time exposed (masks off) (hr:min:sec)	TWA during exposure (ppm)
101	3:19:13	2.46	4:00:18	55.12
102	1:50:04	3.30	4:00:15	52.97
103	2:36:05	3.39	3:59:14	105.46
104	2:09:08	6.13	4:00:08	102.54
105	0:57:03	11.97	4:00:09	101.41
106	1:32:03	5.37	4:00:09	49.27
107	NA	NA	~4:00:00	~101.99
108	NA	NA	~4:00:00	~101.99
109	2:09:06	5.13	4:05:12	97.71
110	2:05:11	8.99	3:59:12	101.04
111	1:38:06	11.81	3:59:17	103.32
201	3:24:13	3.63	4:00:18	55.21
202	1:55:04	5.18	4:00:15	53.10
203	2:41:05	6.44	4:00:14	105.51
204	2:14:08	9.54	4:00:08	102.64
205	1:02:03	17.51	4:00:09	101.50
206	no subject			
207	NA	NA	~4:00:00	~101.99
208	NA	NA	~4:00:00	~101.99
209	2:14:06	8.42	4:05:12	97.76
210	2:10:11	11.24	3:59:12	101.12
211	1:42:06	15.89	3:59:17	103.40

TWA - Time Weighted Average

LITERATURE SEARCHES FOR PHYSIOLOGICAL PARAMETERS

This literature search was performed with the intent of gathering physiological parameters used in PBPK modeling. Although the PBPK models in use by the Toxicology Division already contained estimated values for all fields, measured data are preferable. The search objective was to gather both measured and estimated human physiological data needed in PBPK modeling such as body weight, percent body fat, organ volumes and organ blood flows. These physiological parameters are listed below:

- age
- sex
- ethnicity
- body weight
- volumes (expressed as a fraction of body weight): body fat, slowly perfused organs, rapidly perfused organs, liver, lung and kidney
- blood flow rates (expressed as a fraction of cardiac output): body fat, slowly perfused organs, rapidly perfused organs, liver, lung and kidney
- cardiac output
- breathing rate

Medline (1966 to 1995) and Toxline (1990 to 1995) were searched for this data. Abstracts were reviewed by the PI and articles were selected for review. The key terms summarized in Table 3 were used in the search for physiological parameters and PBPK models. Various textbooks were also used to gather human physiological parameters. Published resources were retrieved from area libraries. Once literature was gathered, article reference lists were reviewed for older sources of valuable information.

METHOD FOR PHYSIOLOGICAL PARAMETER EVALUATION

Both measured and default physiological parameter values were obtained from the articles and entered into spreadsheets. Information regarding how default estimates were made was also included. The values from all studies were then converted to standard units. Organ volumes had to be expressed as percent body weight and blood flow as percent cardiac output. Both the measured and default physiological parameters found in the literature are compiled in Attachment VI. For this task alone, 90 articles were obtained and reviewed.

Table 3
Summary of Literature Searches for Physiological Parameters

	Databases Accessed	Age-Factor	Body-Weight	Chloral (75-87-6, 302-17-0)	Dichloroacetic, Dichloroacetate (79-43-6, 13425-80-4)	Human	Kidney	Lung	Reference-Values	Simulation	Trichloroethanol (115-20-8)	Trichloroethylene, Trichloroethene (79-01-6)
Body-Composition	a	a 1							a 1			
ICRP Reference Man	a											
PBPK	a b			b	b	b					b	b
Volume	a						a					
Individual Authors (Referenced in Articles)	a		a					a		a		

a Medline 1966-95 Toxline 1990-95
b Medline 1966-82, 1990-95 Toxline 1990-95
1 Refined with Human*

SUMMARIZATION OF DCA DOSING STUDIES

Human and animal DCA studies were collected and summarized into a quick review article for reference by the PI, who serves on the International Life Science Institute's expert panel to evaluate chloroform and DCA as case studies for application of EPA's proposed cancer guidelines for carcinogen risk assessment. Additional literature searches were conducted for human data that may have been missed during the focused PBPK data search. Due to the limited number of human studies on DCA, toxicity and carcinogenicity data from available animal studies and review articles were also summarized. The study material summarized included information such as dose level and technique, clinical and non-clinical responses and tumor incidence. Eighteen study summaries are presented below.

Human Data Summaries

Curry SH, Chu PI, Baumgartner TG, Stacpoole PW. 1985. Plasma concentrations and metabolic effects of intravenous sodium dichloroacetate. Clin Pharmacol Ther. 37:89-93.

Eleven subjects (seven healthy men and five healthy women) between the ages of 22 and 57 received five doses of 10, 25 or 50 mg/kg intravenous sodium dichloroacetate (DCAC) at 2-hour intervals. Three subjects received the 10 mg/kg DCAC, five subjects (which included one individual from the 10 mg/kg dosing group) received 25 mg/kg and the remaining four received 50 mg/kg. Baseline glucose and lactate levels were established after an overnight fast.

The male and female subjects were unevenly distributed over the three dose levels with respect to sex, but the difference was not significant ($\chi^2 = 5.04$). Blood DCA concentrations rose and fell during and after each infusion. There was variation between subjects, even among those receiving the same dose. Lactate levels fell as the result of DCAC treatment.

With repeated doses of 50 mg/kg DCAC, mean 24-hour urinary oxalate excretion was approximately 200 mg/g creatinine, which is about seven times the daily excretion rate for healthy subjects (29.5 mg/g creatinine).

Blood pressure and pulse remained stable. Subjects receiving 10 or 25 mg/kg doses did not experience any unpleasant effects. After the second or third infusion, the three subjects who received 50 mg/kg experienced mild drowsiness that lasted several hours after the final dose.

Lukas G, Vyas R, Brindle SD, LeSher AR, Wagner WE. 1980. Biological disposition of sodium dichloroacetate in animals and humans after intravenous administration. J Pharm Sci. 69(4):419-421.

^{14}C-Sodium dichloroacetate (DCAC) was administered to rats, dogs and humans. Plasma and urine samples were collected over time. Three male Sprague-Dawley rats (169-179 g) were given 100 mg/kg ^{14}C-sodium DCAC (in a 10% aqueous solution) intravenously (iv) and blood samples were collected. Following the 100 mg/kg iv dose to the three rats, maximal plasma concentrations of unchanged sodium DCAC ranged between 120 and 164 μg/mL. Subsequent declines of plasma concentrations occurred with half-lives of 2.1-4.4 hours. Declines of

radioactivity were slow. Apparent half-lives of 21-36 hours indicated extensive metabolism and slow elimination of metabolites.

Two male beagles (9-10.5 kg) were given 100 mg/kg ^{14}C-sodium DCAC (in a 20% aqueous solution) intravenously. The maximum concentrations of 447 and 508 μg/mL were measured in plasma at 5 minutes. Subsequent declines were slow with a half life of 17.1 - 24.6 hours, also indicating extensive metabolism and slow elimination.

Four healthy humans were dosed after an overnight fast. Subjects 1 and 2, ages 42 and 38 both weighed 70 kg and received a 10 mg/kg dose in 100 mL of saline infused over 20 min. Subjects 3 and 5, ages 52 and 26 years (80 and 83 kg, respectively) received 20 mg/kg DCAC. No subjective or objective changes or signs or clinical activity were noted in any human subject upon intravenous infusion of either the 10 or 20 mg/kg doses of ^{14}C-sodium DCAC. The highest plasma concentrations were obtained immediately after the end of the infusions. Subjects 1 and 2 receiving 10 mg/kg had maximum values of 20 and 35 μg/mL, respectively. Maximum concentrations of 57.3 and 74.9 μg/mL were seen in Subjects 3 and 4 after 20 mg/kg. Human plasma levels declined mono-exponentially over a 200-500 fold concentration range, corresponding to a range of 7-9 hour half-lives. Metabolites were not explored in detail in this study.

Urinary excretion of unchanged ^{14}C-sodium DCAC was negligible after the first 8 hours; in all humans, cumulative excretion amounted to considerably less than 1% of the dose. The intrinsic clearance of ^{14}C-sodium DCAC was considerably greater than, and the elimination presumably limited by, blood flow in subjects receiving 10 mg/kg. In subjects receiving 20 mg/kg, intrinsic clearance was lower. A doubling of the dose led to an approximately seven-fold decrease in intrinsic clearance, yet the systemic (plasma or blood) clearance values decreased only by a factor of two or three.

This study demonstrates the difficulty in predicting the toxicity of therapeutic drug dosage in humans from comparatively large doses used in animal toxicity testing due to differences in elimination rates between species. The elimination rate in humans was dose dependent and limited by hepatic blood flow, whereas elimination of high doses was not flow limited in rats and dogs since hepatic blood flow greatly exceeded intrinsic clearance.

Wells PG, Moore GW, Rabin D, Wilkinson GR, Oates JA, Stacpoole PW. 1980. Metabolic effects and pharmacokinetics of intravenously administered dichloroacetate in humans. Diabetologia 19:109-113.

DCAC was infused over 30 minutes to 16 healthy subjects (15 male, 1 female, ages 25 to 45 years, mean age 30 and within 10% of ideal body weight) following an overnight fast. Doses of 1, 5, 10, 15, 20, 25, 30, 35 and 50 mg/kg were administered in increasing strength. Blood samples were taken every 30-60 minutes over 12 hours. Plasma was separated and analyzed by gas chromatograph (GC) for pH, glucose, lactate, alanine, bicarbonate and DCA concentrations.

Plasma concentrations of DCA were linearly related to dose ($r = 0.98$, $p < 0.001$) up to 30 mg/kg, above which 4 of 7 subjects had disproportionately high plasma DCA concentrations,

indicating nonlinear pharmacokinetics. This may be expected with increasing dosages or multiple dosing. Plasma clearance of DCA decreased with doses greater than 20 mg/kg.

At 1 and 10 mg/kg, DCAC had no effect on lactate, glucose and alanine. Maximum lactate depression for DCAC doses between 15 and 50 mg/kg occurred 1 to 2 hours after beginning of infusions. Lactate levels then remained below baseline for 8 to 10 hours and returned to baseline by 12 hours. Within 2 hours of administration of the maximally effective dose (35 mg/kg), plasma lactate concentrations fell 75% below baseline, which blood glucose did not change. With both 35 ($n = 3$) and 50 ($n = 6$) mg/kg doses, plasma alanine concentrations decreased 50% in 1 hour, remained maximally depressed for 6 hours, and were still below baseline at 12 hours. Decreases in plasma lactate and alanine were linearly correlated with DCAC dose and peak plasma concentrations from doses of 20 mg/kg up to 35 mg/kg ($r = 0.93$, $p < 0.01$). Glucose levels fell slightly after 12 hours in subjects receiving the 50 mg/kg dose ($n = 6$). Plasma bicarbonate, pH, blood pressure, pulse and ECG did not change at any DCAC dose. One subject complained of drowsiness following a dose of 50 mg/kg.

Animal Data Summaries

Pharmacokinetics

Ribes G, Valette G, Loubatieres-Mariani MM. 1979. Metabolic effects of sodium dichloroacetate in normal and diabetic dogs. Diabetes 28:852-857.

In an acute exposure study, mongrel dogs were dosed with 150 mg/kg DCAC through gastric intubation and observed for 48 hours. Normal dogs (14 to 18 kg) were fasted for 18 hours prior to dosing, but were fed at 10 and 32 hours after dosing. Diabetes was produced in dogs (12 to 16 kg) through iv administration of 50 mg/kg alloxan. These dogs had been diabetic at least two months prior to the experiment and insulin was withheld 72 hours prior to dosing. Nine dogs received DCAC and six received 20 mL 9% sodium chloride via intubation.

To determine the effects of repeated exposure, normal dogs received 150 mg/kg DCAC for seven days with a meal. Three diabetic dogs received subcutaneous insulin with 75 mg DCAC/kg orally for seven days. Fasting blood levels were taken 18 hours after daily meals.

In normal dogs, acute exposure resulted in rapid decreases in blood lactate, pyruvate and triglyceride levels (35, 27 and 62% of starting values, respectively). Decreases persisted for 24 to 48 hours. Blood glucose did not begin to decrease until four hours post exposure; the decrease was significant at 24 ($p<0.01$), 26 ($p<0.01$) and 28 hours ($p<0.05$). Repeated exposure resulted significantly lower ($p<0.001$) levels of blood glucose after 24 hours; the decreased levels persisted two days post exposure. Blood lactate, pyruvate and triglyceride levels again decreased rapidly (36, 20 and 20% of starting values, respectively) and persisted for four to six days or longer. Plasma cholesterol was reduced ($p<0.001$), recovering five days post exposure. Blood β-hydroxybutyrate and acetoacetate levels increased rapidly and returned to basal values on the sixth post exposure day. Ketone bodies were not present in the urine of normal dogs.

In diabetic dogs, blood glucose levels were decreased significantly ($p<0.05$) from sodium chloride controls at four hours after acute exposure. Glucose was decreased to a maximum of 80% of the starting value and the decrease persisted longer than 24 hours. Blood lactate, pyruvate and oxaloacetate levels decreased rapidly and stayed low for 24 to 48 hours. DCAC did not significantly lower the plasma lipid or blood ketone concentrations as compared to the controls. Urinary levels of acetone and β-hydroxybutyrate were not decreased. Glucosuria levels were significantly decreased ($p<0.02$); the decrease persisted for 48 hours. Repeated exposure resulted in blood glucose decreases ($p<0.001$) which lasted 48 hours post exposure. Blood lactate, pyruvate and oxaloacetate also rapidly decreased. Plasma lipids (triglyceride, cholesterol and total lipids) were all significantly ($p<0.001$) decreased. Blood β-hydroxybutyrate and acetoacetate levels were not decreased. Glucosuria decreased rapidly while urinary β-hydroxybutyrate and acetone increased.

Ward RA, Wathen RL, Harding GB, Thompson LC. 1985. Comparative metabolic effects of acetate and dichloroacetate infusion in the anesthetized dog. Metabolism 34(7):680-687.

Five dogs (13 to 36 kg) were exposed to saline (10 mmol/hr-kg), acetate (10 mmol/hr-kg) or DCAC (1 or 10 mmol/hr-kg) for 60 minutes via intravenous infusion. Prior to exposure, the dogs were fasted for 48 hours, anesthetized and infused with saline (control period) for 30 minutes. Following exposure, saline was infused for a 30 minute recovery period. All significance levels are $2p<0.05$.

The low dose of DCAC (1 mmol/hr-kg) resulted in increased blood bicarbonate levels (over baseline and saline control) and increased arterial serum potassium and inorganic phosphorus levels over baseline levels. Low doses decreased arterial blood lactate and pyruvate over baseline and saline control levels. Arterial citrate levels were decreased while acetoacetate levels increased over baseline levels. Arterial alanine was dramatically decreased from baseline levels.

High doses of DCAC (10 mmol/hr-kg) increased arterial CO_2 partial pressure as compared to baseline and saline control levels. Arterial serum sodium and inorganic phosphorus increased over baseline and saline control values; serum potassium levels increased over baseline levels. DCAC decreased arterial pyruvate and citrate over baseline and control values while it increased acetoacetate concentrations above baseline. Arterial alanine concentrations, free fatty acids and plasma insulin levels decreased as compared to baseline.

Lin EL, Mattox JK, Daniel FB. 1993. Tissue distribution, excretion and urinary metabolites of dichloroacetic acid in the male Fischer 344 rat. J Toxicol Environ Health. 38:19-32.

Two doses of 2-(^{14}C)-DCA (28.2 and 282 mg/kg), which are approximately 1/100 and 1/10 of the LD_{50} (Smyth, 1951), and one dose level of 1-(^{14}C)-DCA (282 mg/kg) were administered by oral gavage to Fischer 344 male rats (in groups of 4,5 and 6 respectively). The dosing solutions were prepared by mixing labeled and unlabeled DCA so that each animal received

about 20 μCi of ^{14}C (40-450 μCi/mmol). The rats weighed between 180-240 g. They were fed water and chow throughout the experiment, except during an overnight fast before dosing.

Exhaled CO_2 was collected in ethanolamine and exhaled volatile organics were adsorbed using charcoal tubes and later extracted with methanol. Feces and intestinal contents were extracted. Urine, ethanolamine, methanol extracts of charcoal tubes and water extracts of feces were analyzed for radioactivity. At termination, as much blood was collected as possible. Whole organs and samples of muscle, skin and adipose (testicular) were removed and weighed. Blood and tissue digest were analyzed for radioactivity.

The major routes of disposition for DCA were urinary excretion and exhalation of CO_2. Expiration of CO_2 accounted for ~29% of the 282 mg/kg 1-DCA dose and ~25-34% of the 28.2 and 282 mg/kg 2-DCA doses. Only about 2% of the 282 mg/kg doses of 1- and 2-DCA and <1% of the 28.2 mg/kg dose of 2-DCA were recovered from the feces after 48 hours. Exhaled volatile organics accounted for 0.1% of the DCA in all cases. About 33.3 and 35.2% of the dose was cumulatively excreted in urine and 28.8 and 25.0% was exhaled as CO_2 for 1- and 2-DCA, respectively, at the 282 mg/kg dose. There was not a significant difference between the excretion patterns of the 1- and 2-DCA doses ($p < 0.01$; however, compared to the 28.2 mg dose of 2-DCA, a significantly greater percentage of the dose was expired as CO_2 (34.4% vs. 25%) and a lesser percentage was excreted in urine (12.7% vs. 35.2%) and feces (0.8% vs. 2.0%) at 28.2 mg/kg relative to the 282 mg/kg dose, respectively.

Analysis of urinary metabolites by HPLC showed oxalic acid, glycolic acid, and glyoxylic acid in the urine, accounting for about 10% and 22% of the administered dose of 1- and 2- DCA, respectively. At termination, the tissues retained 20.8% of the ^{14}C associated with 1-DCA (282 mg/kg dose) and 26.2 and 36.4% of that with 2-DCA, 282 and 28.2 mg/kg, respectively. Liver and muscle tissues contained the highest amounts, followed by the skin, blood and intestines. Significantly higher percentages of the dose were retained in tissues of rats receiving the lower 2-DCA dose compared to the higher 2-DCA dose.

Yount EA, Felten SY, O'Connor BL, Peterson RG, Powell RS, Yum MN, Harris RA. 1982. Comparison of the metabolic and toxic effects of 2-chloropropionate and dichloroacetate. J Pharmacol Exper Ther. 222(2):501-508.

Acute and subchronic toxicity studies of 2-chloropropionate and DCAC were conducted on male Wistar rats and male and female ICR mice. Blood samples were taken, but urine samples were not collected. Five dose levels from 24 to 53 mmol/kg DCAC were administered by gavage to five male and five female mice. Mice were observed for one week for mortality. The oral LD_{50} values were 15.4±1.1 mmol/kg body weight. To study prolonged toxicity, DCAC was feed orally to male rats (0.04 mol/kg of feed) for 12 weeks. Rats feed DCAC consumed less food and gained less weight than control rats. Hind limb weakness and abnormal gait were observed in the rats within two to four weeks after DCAC was added to feed. The absolute weights of the spleen, lungs, heart, testes plus epidermis and brain were significantly less ($p < 0.05$) than the weights of these organs in the control group. Glucose levels were approximately the same in the control and DCAC groups. Free glycerol in plasma was not significantly different from the control group.

Nerve conduction velocities were significantly less than in the control group. Cross sections of the tibial nerve showed that the group treated in DCAC had significantly smaller diameters of the tibial nerves than those of the control groups, indicating possible impaired nerve maturation.

Larson JL, Bull RJ. 1992. Metabolism and lipoperoxidative activity of trichloroacetate and dichloroacetate in rats and mice. Toxicol Appl Pharmacol. 115:268-277.

Male F344 rats (331 ± 24g) and male B6C3F1 mice (27± 2 g) were administered 5,20 or 100 mg/kg [C^{14}]trichloroacetate (TCAC) or [C^{14}]DCAC as a single oral dose in water after a 24 hour fast. Blood was collected over time for the 20 and 100 mg/kg doses. Radioactivity in urine, feces, plasma, exhaled air and carcasses was counted. DCAC was much more extensively metabolized than TCAC. In both species, 48 to 65% of the initial dose of TCAC was excreted unchanged in urine, whereas < 2% of DCAC was excreted unchanged in urine. The relative amount of unresolved nonchlorinated acids, as a percent of initial dose recovered in urine from DCAC dosed rodents, was about twice that of TCAC dosed rodents. Nonchlorinated acids accounted for 10-15% of the overall DCAC dose. Thiodiacetic acid in urine represented 6-10% of the initial dose.

Exhalation of CO_2 accounted for 24-30% of the initial dose of DCAC in rats (representing the major excretory route for DCAC). This compared to 6-8% of initial dose of TCAC in rats. Most radio-labeled CO_2 was recovered within two hours from dosing. Mice only excreted about 2% of the dose as CO_2.

Blood concentration curves for the two species were similar, but were markedly greater in rats. Peak plasma concentrations of TCA ranged from 3 to 60 fold higher than peak plasma concentrations of DCA in comparably dosed animals from the same species. The half life values were also greater in TCAC-treated than in DCAC-treated animals.

To evaluate the ability of acute doses of TCAC and DCAC to elicit a lipoperoxidative response, additional groups of mice were administered 0, 100, 300, 1000 and 2000 mg/kg TCAC and DCAC. Both TCAC and DCAC enhanced the formation of hepatic thiobarbituric acid-reactive substances in a dose-dependent manner; however TCA's effect was greater.

Carcinogenicity/Toxicity Studies

Snyder RD, Pullman J, Carter JH, Carter HW, DeAngelo AB. 1995. *In vivo* administration of dichloroacetic acid suppresses spontaneous apoptosis in murine hepatocytes. Cancer Res. 55:3702-3705.

Male B6C3F1 mice were exposed to DCA at 0.5 or 5.0 g/L in drinking water for 5, 10, 15, 20, 25 or 30 days. DCA significantly depressed apoptosis in hepatocytes as compared to age-matched controls. Through regression analysis, apoptosis was found to decrease in the untreated controls over the 30 day period; apoptotic frequency ranged from 0.09 to 0.04%. The 0.5 g/L DCA dose group was found to have a similar, but more depressed, apoptosis trend. Apoptosis frequency was significantly different from the control on days 5, 15, 25 and 30 days and ranged from 0.06 to 0.02%. The 5.0 g/L group reached the maximum depression of apoptosis (0.01%) at 5 days. Depression persisted for the duration of exposure, ranging from

0.03 to 0.01%. Apoptosis frequency was significantly depressed on days 5, 10, 15, 25 and 30 ($p<0.02$). These results support the hypothesis that the carcinogenicity of DCA involves suppression of the liver's ability to remove initiated cells through apoptosis.

Daniel FB, DeAngelo AB, Stober JA, Olson GR, Page NP. 1992. Hepatocarcinogenicity of chloral hydrate, 2-chloroacetaldehyde and dichloroacetic acid in the male B6C3F1 mouse. Fundam Appl Toxicol. 19:159-68.

Chloral hydrate, 2-chloroacetaldehyde and DCA were administered to male B6C3F1 mice over a period of 104 weeks. Mice ($n = 58$) were exposed to approximately 93 mg DCA/kg-day (0.5 g/L) via drinking water. The mean daily water consumption volume was slightly decreased as compared to controls but was not statistically significant.

Exposure resulted in increased ($0.01<p<0.03$) liver and relative liver weights at 104 weeks. Of the 24 animals examined, 33% had hepatocellular necrosis and hyperplasia. Fully 100% of the 24 had cytoplasmic vacuolization; 92% had cytomegaly and 46% were found to have chronic active inflammation. Liver tumor incidence was significantly ($p<0.01$) increased; 63% of exposure survivors presented with hepatocellular carcinomas and 42% had adenomas. The prevalence of carcinomas plus adenomas was 75%.

Bull RJ, Sanchez IM, Nelson MA, Larson JL, Lansing AJ. 1990. Liver tumor induction in b6c3f1 mice by dichloroacetate and trichloroacetate. Toxicology. 63:341-359.

Male and female B6C3F1 mice were exposed via drinking water to 1 or 2 g/L of DCAC or trichloroacetate daily for up to 52 weeks. Hepatoproliferative lesions were significantly increased for both substances; lesions included hepatocellular nodules, adenomas and carcinomas.

DCAC did not produce any carcinomas in animals exposed for 37 or 52 weeks (sacrifice time for both groups was 52 weeks). DCAC induced lesions increased sharply and disproportionally with increase in total dose over time. In the 1 g/L-dy, 52 week exposure group, 2 of 11 male mice had lesions. At 2 g/L-dy for 52 weeks, 23 of 24 male mice bore lesions while 7 of the 11 male mice exposed for 37 weeks had lesions. Three of the ten female mice exposed to 2 g/L-dy for 52 weeks responded with hyperplastic nodules observable only on microscopic examination.

Both male and female DCAC treated mice had enlarged livers and significantly ($p<0.05$) increased liver weights with cytomegaly, massive accumulation of glycogen within hepatocytes and multiple focal points of necrosis. Although there was substantial reversal of liver damage in the 37 week exposed male mice, liver weights were still significantly increased at the 52 week sacrifice. Tumorigenesis of DCAC appears to depend on stimulation of cell division after hepatic damage.

Herren-Freund SL, Pereira MA, Khoury MD, Olson G. 1987. The carcinogenicity of trichloroethylene and its metabolites, trichloroacetic acid and dichloroacetic acid, in mouse liver. Toxicol Appl Pharmacol. 90:183-189.

Male B6C3F1 mice were administered trichloroethylene, trichloroacetic acid or DCA with or without an initiator to determine the carcinogenic potential of these compounds. The initiator, ethylnitrosourea, was administered intraperitoneally at 0 or 2.5 μg/g to 15 day old mice; 2 μL/g sodium acetate was injected as the solvent control. DCA was administered in the drinking water at 2 or 5 g/L for 61 weeks starting at 28 days of age.

Noncancer effects of DCA included increased ($p<0.001$) liver weight and relative liver weights in the initiated 2 g/L dose group ($n = 29$). Liver weights were also increased in the initiated 5 g/L dose group ($n = 32$); kidney weights but not relative kidney weights and body weights were decreased at $p<0.05$ and $p<0.001$ significance levels, respectively. DCA dosing alone without initiation ($n = 26$) resulted in decreased body and kidney weights and increased liver and relative liver weights, all at $p<0.001$ significance.

The 5 g/L DCA dose induced hepatocellular carcinomas in 81% of the mice without initiation. Adenomas and the number of adenomas per mouse was also significantly increased at 5 g/L. Initiation of 2 or 5 g/L DCA with 2.5 μg/g ethylnitrosourea resulted in 66 or 78% carcinomas, respectively, as compared to just 5% incidence of carcinomas in the initiated controls. DCA is therefore a complete hepatic carcinogen.

Daniel FB, DeAngelo AB, Stober JA, Olson GR, Page NP. 1992. Hepatocarcinogenicity of chloral hydrate, 2-chloroacetaldehyde and dichloroacetic acid in the male B6C3F1 mouse. Fundam Appl Toxicol. 19:159-169.

Male B6C3F1 mice were exposed to chloral hydrate, 2-chloroacetaldehyde (CAA) and DCA in drinking water over 104 weeks. The drinking water solutions were GC analyzed biweekly to determine actual concentrations of test chemicals. The mean daily ingested dose of DCA was 93 mg/kg-day. The dose levels selected were estimated to be at a level in which minimal or no taste aversions would occur, yet at a level which would approximate a maximum tolerated dose. Evaluations included mortality, body weight, organ weights, gross pathology and histopathology. Prevalence rates for each treatment group were calculated as the ratio of the number of animals with a specific lesion to the number of animals examined. In addition to the separate analysis of each lesion type, carcinomas, adenomas and nodules were combined for an analysis of the total proliferative lesions. All tumors were detected at necropsy and were not responsible for premature mortality.

There were no significant difference in the mortality observed in the DCA and water (control) groups. No specific non-neoplastic lesions in tissues other than the liver were seen. The most prominent non-neoplastic liver lesions were hepatocellular cytomegaly and vacuolization noted in DCA-treated animals. At the 104-week terminal necropsy 15 of the 24 (63%) DCA-treated animals had carcinomas compared to 2 of 20 (20%) in the control group (significantly different at $p \leq 0.01$). Three additional DCA-treated animals and one animal in the control group displayed adenomas for a total tumor prevalence of 75% and 15%, respectively. DCA appeared to exhibit a threshold-like response, with the threshold lying between 0.5 and 2 g/L.

DeAngelo AB, Daniel FB, Stober JA, Olson GR. 1991. The carcinogenicity of dichloroacetic acid in the male B6C3F mouse. Fundam Appl Toxicol. 16:337-347.

Male B6C3F mice (21 days old) were weighed and randomly distributed into groups (N=50) and dosed with drinking water containing 2 g/L sodium chloride (control group), 0.05, 0.5 and 5 g/L DCA. Mean daily doses of 7.6, 77, 410 and 486 mg/kg-dy were calculated for 0.05, 0.5, 3.5 and 5 g/L DCA treatments, respectively. Water intake and body weights were recorded weekly during the first month and monthly afterward. At 4 (3.5 g/L DCA),15, 30 and 45 weeks, 5 animals from each treatment group were killed by CO_2 asphyxiation. At 60 weeks, 9 from the control, 0.05, 0.5 g/L DCA and 30 from the 5 g/L DCA groups were killed. Remaining mice from the control, 0.05 g/L DCA, and 0.5 g/L DCA groups were continued on treatment for 15 more weeks. Liver, kidney, testes and spleen were weighed and examined for lesions or irregularities.

Mice receiving 5 g/L DCA restricted their intake of drinking water to 60% as compared to the controls. The mean daily dose for this group was high at the beginning of the exposure period. Those drinking 5 and 3.5 g/L had significantly lower final body weights (17 and 13%, $p < 0.001$) than the mean body weights of the control. Relative liver weights were increased 351, 230 and 118% (5, 3.5, and 0.5 g/L groups at 75 weeks). No changes in the weights of testes or spleen were observed.

Three types of proliferate lesions were seen in the livers: hyperplastic nodules, hepatocellular adenomas and hepatocellular carcinomas. A significant positive dose-related trend was found between incidental live tumors and age ($p<0.001$). The prevalence of liver tumors in each group increased precipitously and exceeded 90% by 60 weeks. Neoplasia was first observed in the 0.5 g/L DCA group at 45 weeks. Tumor multiplicity was characteristic of DCA-induced carcinogenicity.

Cicmanec JL, Condie LW, Olson GR, Wang SR. 1991. 90-day toxicity study of dichloroacetate in dogs. Fundam Appl Toxicol. 17:376-389.

Beagle dogs were orally administered 12.5, 39.5 or 72 mg DCAC/kg-day in gelatin capsules for 90 days. Forty dogs were used; five females (6.1-9.4 kg) and five males (8.6-13.6 kg) were used in each dose group. Blood samples were taken every 15 days.

Total RBC counts were decreased ($p<0.05$) in the high dose females at 30, 45, 60 and 90 days; high dose males had decreased RBCs from day 30 until completion. Hemoglobin levels were also decreased in the high dose groups; female hemoglobin counts were down ($p<0.03$) on days 45, 60 and 90 whereas male counts were low ($p<0.01$) from day 30 until the end of exposure. Serum LDH levels were increased ($p<0.01$) in high dose females on days 30 and 45. Male LDH levels were high ($p<0.01$) on days 75 and 90.

External presentations during dosing included conjunctivitis and clear ocular discharge in nearly all treated and some control animals. The discharge became purulent and the conjunctivitis increased in high dose dogs. Diarrhea was observed among some of the mid and high dose dogs, progressing in some to necessitate supportive care. At 45 days, dyspnea was noted in four mid and 8 high dose animals. The severity of dyspnea increased over time; all high dose

dogs had severe symptoms by 90 days. Several high dose dogs presented with partial hind limb paralysis; paralysis was persistent but not progressive. One female and two males from the high dose group died on days 50, 51 and 74, respectively. Cause of death was pneumonia and dehydration.

At necropsy, relative liver weight were found to be significantly ($p<0.05$) increased in both male and female dogs at all dose levels. Relative kidney weights were also increased ($p<0.03$) in the mid and high dose groups for both male and female dogs. Chronic hepatitis and vacuole changes were found in animals of all dose groups. Many of the high and some of the mid dose groups responded with suppurative bronchopneumonia and chronic pancreatitis. Mild vacuolization of the myelinated white tracts in the cerebrum, cerebellum and spinal cord were observed in several high dose dogs as well as a few mid and low dose animals. Males in all dose groups showed evidence of testicular germinal epithelium degeneration and syncytial giant cell formation.

Other/Review Articles

Stacpoole PW, Gonzalez MG, Vlasak J, Oshiro Y, Bodor N. 1987. Dichloroacetate derivatives: Metabolic effects and pharmacodynamics in normal rats. Life Sci. 41:2167-2176.

Nine male Sprague-Dawley rats (210±10g) were fasted for 24 hours prior to a single gavage dose of saline, 100 mg DCAC/kg in saline, or one of four DCAC derivatives equivalent to 100 mg/kg DCAC anions. Acute dosing resulted in universal decrease ($p<0.001$) of serum glucose and lactate by DCAC or its derivatives as compared to controls. DCAC maximally decreased glucose by 18%; the maximum decrease occurred at six hours post exposure. DCAC decreased glucose levels for 18 hours. DCAC maximally reduced lactate levels by 36% at 4 hours; the effect lasted more than 24 hours. DCAC plasma concentration peaked at approximately 24 minutes (maximum concentration) and again at 12 hours.

Stacpoole PW. 1989. The pharmacology of dichloroacetate. Metabolism. 38(11):1124-1144.

Pharmacokinetics

It is assumed that DCAC undergoes removal of chloride by cytochrome P450-dependent microsomal dehalogenases present in liver and possibly in other tissues, and is hydroxylated to glyoxylate (Pohl LR *et al.* 1978. Biochem Pharm. 27:335-341; Halpert J *et al.* Biochem Pharm. 30:1366-1368). However less than 5% of an oral or iv dose of 50 mg/kg DCAC administered to healthy volunteers is excreted unchanged or as oxalate in urine and negligible quantities are bound to plasma proteins or taken up by red blood cells (Wells PG *et al.* 1980. Diabetologia 19:109-113; Curry SH *et al.* 1985. Clin Pharm Ther. 37:89-93).

Wells *et al.* (1980) and Curry *et al.* (1985) reported that peak plasma levels in humans following an initial oral or intravenous DCAC dose of 50 mg/kg are approximately 150 μg/mL, or about 1 mmol/L, and has a half-life in plasma between 0.5 and 2 hours, similar to that obtained after a

single intravenous infusion dose. Chu also reported no observed difference in the area under the plasma concentration curve for DCAC between oral and iv doses, indicating equivalent bioavailability. The renal clearance of the drug is low (approximately 4 mL/hr) and is independent of urinary flow rate or pH (Chu PI. 1987. Pharmacokinetics of DCAC. Doctoral Dissertation. University of Florida).

Wells *et al.* (1980) reported single (1 to 50 mg/kg) iv doses to exhibit nonlinear kinetics at dose $\geq$ 35 mg/kg. Intravenous administration of up to 50 mg/kg DCAC in normal subjects demonstrated that the drug is metabolized increasingly slowly with repeated dosing, consistent with progressive changes in $t_{1/2}$, V_{max} and K_m. In these studies, first order decay kinetics were retained, presumably because a high enzyme to substrate concentration ratio was preserved. In healthy individuals, both the area under the plasma concentration curve for DCAC and the increase in urinary oxalate were linearly related to dose, with a mean DCAC apparent volume of distribution of 0.30 L/kg that was independent of dose (Curry *et al.*, 1985). In patients with hypotension and lactic acidosis, however, the change in the volume of distribution, was directly related to dose.

Toxicology

The LD_{50} of DCAC in most species is 1-5 g/kg orally or 0.5-1 g/kg iv. Death is usually from progressive central nervous system depression. Early chronic toxicity studies with daily iv DCAC doses between 100 and 250 mg/kg in rats for greater than 30 days were nontoxic. Chronic doses exceeding 1g/kg usually lead to anorexia and weight loss. When given doses greater than 50 mg/kg DCAC orally for weeks, rats and dogs exhibit neurotoxicity by reversible hind limb motor weakness and demyelination of cerebral and cerebellar white matter.

Katz R *et al.* (1981. Toxicol Appl Pharmacol. 57:273-287) reported morphologic changes in testes of rats and irreversible lenticular opacities in beagle dogs with doses as low as 75 mg/kg of DCAC. Subsequent studies, however, have not confirmed these affects even with rats receiving up to 1.1 g/kg DCAC.

DCAC stimulates at least two thiamine-dependent enzymes *in vivo*. Chronic DCAC treatment may induce thiamine deficiency through an increased demand for this vitamin. Co-administration of thiamine with DCAC to rats significantly reduced the incidence of hind limb weakness seen with both DCAC and thiamine deficiency. Oxalate excretion increases in humans and rats treated with DCAC, but is reduced in animals concurrently supplemented with thiamine. Oxalate is a metabolite known to cause peripheral neuropathy and cataracts.

IARC. 1995. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. WHO. Lyon, France. 63:271-90.

Cancer Studies

The International Agency for Research on Cancer (IARC) was unable to find cancer studies of humans exposed specifically to DCA. Therefore, there is Inadequate Evidence in humans for carcinogenicity of DCA.

IARC cited Herren-Freund *et al.* (1987), Bull *et al.* (1990), DeAngelo *et al.* (1991) and Daniel *et al.* (1992) for DCA cancer studies in animals. They found Limited Evidence of carcinogenicity in laboratory animals. Overall, the IARC lists DCA in Group 3 - Not Classifiable as to its Carcinogenicity to Humans.

Toxic Effects

IARC cited Stacpoole (1989) concerning toxic effects of DCA in humans. IARC reported additionally that drowsiness is a frequent side-effect of DCA use and has been observed in healthy and ill subjects. Reversible (within several weeks) peripheral neuropathy with loss of reflexes and muscle weakness was observed in a hypercholesterolaemia patient taking 50 mg/kg-dy for four months (Moore GW *et al.* 1979. Arteriosclerosis. 33:285-93).

Male and female Sprague-Dawley rats exposed to DCA at 10 to 600 mg/kg-dy for 14 days through drinking water responded with increased excretion of ammonia and changed activities of ammoniagenesis enzymes, which indicates renal adjustment to an acid load. The 600 mg/kg-dy dose group had decreased weight gain (Davis ME. 1986. Environ Health Perspect. 69:209-14).

A 7-week drinking water study in which male Sprague-Dawley rats were dosed with approximately 50 or 1100 mg/kg DCA daily resulted in neurotoxic effects at the higher dose. The 1100 mg/kg-dy caused severe hind limb weakness with demyelination of the cerebral and cerebellar parenchyma. Thiamine depletion was noted and these effects could be partially prevented by providing increased thiamine during dosing (Stacpoole PW *et al.* 1990. Fundam Appl Toxicol. 14:327-37). These results are confirmed in other studies. The hypothesized mechanism includes stimulation of thiamine-dependent enzymes by DCA, which causes increased use of thiamine (Katz R *et al.* 1981. Toxicol Appl Pharmacol. 57:273-87; Yount *et al.*, 1982). A metabolite of DCA in humans and rodents, oxalate, causes peripheral neuropathy and cataracts. The accompanying renal and testicular crystals of oxalate have not been observed with DCA administration, even in high doses (Yount *et al.*, 1982; Stacpoole *et al.*, 1990).

Male Sprague-Dawley rats given approximately 4, 35 or 350 mg/kg-dy for 90 days in the drinking water responded with decreased body weights. The 350 mg/kg-dy dose group also had increased hepatic peroxisomal oxidation activities with histological and biochemical evidence of liver and kidney damage (Mather GG *et al.* 1990. Toxicology. 64:71-80).

In another study, male Sprague-Dawley rats were administered approximately 1100 mg/kg-dy (80.5 mmol/L or 10 g/L) for 90 days. Body weights were decreased and histopathological changes were found in the liver and lung. Additionally, liver weights increased 11% while testicular weights decreased 34% (Bhat HK *et al.* 1991. Fundam Appl Toxicol. 17:240-53).

Male and female Sprague-Dawley rats exposed to 1000 and 2000 mg/L DCA in drinking water for up to 52 weeks showed severe cytomegaly accompanying excessive glycogen accumulation and multiple focal areas which had progressed to necrosis, regenerative cell division and hepatomegaly (Bull *et al.*, 1990; Sanchez IM and Bull RJ. 1990. Toxicology. 64:33-46; Bull RJ *et al.* 1993. Toxicology. 63:341-59).

Beagle dogs dosed with 1100 mg/kg-dy via drinking water for 13 weeks showed signs of ocular toxicity. These dogs are susceptible to drug induced cataracts. This organ specific effect has not been seen in other species or studies (Katz *et al.*, 1981).

Reproductive Effects

IARC could not find available data on human reproductive effects of DCA. DCA and metabolites were found to accumulate in fetuses when pregnant rats were dosed with DCA (Roth AC *et al.* 1991. Teratology. 43:428). Pregnant rats treated with 140 to 2400 mg/kg-dy on days 6 through 15 of gestation resulted primarily in heart and major vessel development problems in fetuses. Other effects included development problems in kidneys and ocular orbits (Randall JL *et al.* 1991. Teratology. 43:454; Smith MK *et al.* 1991. Teratology. 43:453-4; Epstein DL *et al.* 1992. Teratology. 46:225-35; Smith MK *et al.* 1992. Teratology. 46:217-23).

Male Long-Evans rats gavaged with 31.3 or 62.5 mg DCA/kg-dy for 10 weeks presented with sperm and reproductive accessory organ (epididymus and preputial gland) toxicity. Rats dosed with 125 mg/kg-dy had testicular toxicity, decreased late-step spermatid head counts and decreased number of viable implantations at 14 days after mating to unexposed females (Toth GP *et al.* 1992. Fundam Appl Toxicol. 19:57-63).

CONCLUSIONS AND RECOMMENDATIONS

Comprehensive literature searches were found to be effective in identifying sources of physiological parameters as well as TCE and TCE-metabolite human dosing studies. The data extracted from these sources will be used in modeling efforts at Armstrong Laboratory Occupational and Environmental Health Directorate, Toxicology Division. These efforts will be reported separately.

Many TCE and TCE-metabolite human dosing studies located in this effort were of limited use for pharmacokinetic modeling. Many studies lacked time course data; total urine measurements were frequently missing. When costs of collecting time course data are not prohibitive, investigators should consider reporting not only precise initial dosages but also breath, blood, urine and other kinetic data over the complete time course of their experiments. Currently, there is considerable effort to improve PBPK models. Because PBPK studies on humans are few, presentation of actual metabolite data in both tabular and graphic form would provide the scientific community an invaluable resource for validation of new models.

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ATTACHMENT I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Ertle, 1972

Ertle T, *et al.* 1972, Arch Toxikol (29)171-88, Fig 1-2										
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE - Inspired air (ppm)**	**Exposure Duration**	**Time from beginning of exposure (hr)**	**Conc. Total TCOH in Blood (mg/l) Fig 1**	**TCA urinary excretion (mg) Fig 2**	**Cum. Conc. TCA in Urine (mg)**	**Total TCOH urinary excretion (mg)**	**Cum. Conc. Total TCOH in Urine (mg)**
12,m (5 per study)	20-28	57-92		5 dy						
			50	6 hr/dy	6	1.605				
					10	1.143				
					24	0.481	17.933	17.933	122.494	122.494
					30	1.86				
					34	1.359				
					48	0.737	40.293	58.226	154.728	277.222
					54	1.821				
					58	1.411				
					72	0.78	71.934	130.16	158.852	436.074
					78	1.977				
					82	1.527				
					96	0.724	96.39	226.55	210.529	646.603
					102	1.993				
					106	1.599				
					120	0.752	105	331.55	219.579	866.182
					126	0.478				
					144	0.278	82.653	414.203	54.449	920.631
					168	0.13	63.444	477.647	22.522	943.153
			100	6 hr/dy	6	3.218				
					10	2.328				
					24	1.013	15.252	15.252	176.894	176.894
					30	4.928				
					34	2.87				
					48	1.32	79.258	94.51	225.405	402.299
					54	4.36				
					58	3.05				
					72	1.468	142.13	236.64	268.512	670.811

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Ertle, 1972

Ertle T, *et al.* 1972, Arch Toxikol (29)171-88, Fig 1-2										
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE - Inspired air (ppm)**	**Exposure Duration**	**Time from beginning of exposure (hr)**	**Conc. Total TCOH in Blood (mg/l) Fig 1**	**TCA urinary excretion (mg) Fig 2**	**Cum. Conc. TCA in Urine (mg)**	**Total TCOH urinary excretion (mg)**	**Cum. Conc. Total TCOH in Urine (mg)**
					78	4.751				
					82	3.171				
					96	1.632	197.604	434.244	283.034	953.845
					102	4.907				
					106	3.008				
					120	1.496	246.4	680.644	263.859	1217.704
					126	0.873				
					144	0.38	205.186	885.83	85.852	1303.556
					168	0.133	133.393	1019.223	23.304	1326.86
			250 (ave. 50)	12 min/hr, 6 hr/dy	6	1.688				
					10	1.012				
					24	0.441	9.246	9.246	129.177	129.177
					30	1.998				
					34	1.507				
					48	0.579	32.641	41.887	132.524	261.701
					54	2.221				
					58	1.544				
					72	0.826	64.234	106.121	169.091	430.792
					78	2.346				
					82	1.586				
					96	0.775	90.56	196.681	200.399	631.191
					102	2.33				
					106	1.599				
					120	0.695	114.539	311.22	207.251	838.442
					144	0.168	102.814	414.034	56.482	894.924
					168	0.036	64.435	478.469	15.321	910.245

Fernandez, G et al. 1975, Arch. des Maladies Prof. de Med.du Travail. 36(7-8):397-407 Fig. 1												
Subject (#,m,f)	Age (yrs)	Mean Weight (kg)	Conc. TCE - Inspired air (ppm)	Standard Deviation Inspired air (± ppm)	Exposure Duration	Time from beginning of exposure (hr)	Mean % TCE Retained	Absorbed TCE (mg)	Mean Conc. TCE - Expired Air after Exposure (ppm)	Conc. TCE in Aveolar Air (ppm)	Cumula-tive Conc. TCA in Urine (mg)	Cumula-tive Conc. total TCOH in Urine (mg)
Hu, m (Fig 1)	29	76	97	NA	8	0.04	75.70	1169.00		19.45		
						0.13				24.08		
						0.26				28.45		
						0.34				18.48		
						0.60				26.06		
						0.82				19.89		
						1.45				25.21		
						2.01				23.23		
						2.82				23.09		
						3.41				25.29		
						3.81				29.35		
						5.73				26.70		
						5.85				22.48		
						6.04				28.38		
						6.13				18.03		
						7.21				27.80		
						7.33				17.90		
						7.41				22.40		
						7.73				21.72		
						7.84				20.57		
						20.90					24.98	278.03
						48.79					85.19	341.86
						73.15					125.11	409.66
						96.17					173.98	429.27
						121.20					194.22	433.13

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Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Fernandez, 1975

Fernandez, G et al. 1975, Arch. des Maladies Prof. de Med.du Travail. 36(7-8):397-407 Fig. 1												
Subject (#,m,f)	Age (yrs)	Mean Weight (kg)	Conc. TCE - Inspired air (ppm)	Standard Deviation Inspired air (± ppm)	Exposure Duration	Time from beginning of exposure (hr)	Mean % TCE Retained	Absorbed TCE (mg)	Mean Conc. TCE - Expired Air after Exposure (ppm)	Conc. TCE in Aveolar Air (ppm)	Cumula-tive Conc. TCA in Urine (mg)	Cumula-tive Conc. total TCOH in Urine (mg)
						145.20					209.41	436.49
						169.56					225.39	438.63
						192.94					236.16	439.47
						217.49					244.11	439.08
						239.45					250.61	
						264.96					258.26	
						286.58					262.23	
						311.26					265.46	
						335.40					266.63	
						359.54					267.96	
						382.54					270.38	
						406.34					270.76	
						429.38					270.97	
						453.58					270.41	
						476.62					270.47	
						501.58					270.08	
Ca, m (Fig 1)	27	74	97	NA	8	0.05	70.80	1046.00		35.00		
						0.13				35.16		
						0.23				25.46		
						0.73				32.86		
						2.01				25.00		
						2.21				30.47		
						3.35				30.13		
						3.42				30.15		

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Fernandez, 1975

Fernandez, G et al. 1975, Arch. des Maladies Prof. de Med.du Travail. 36(7-8):397-407 Fig. 1												
Subject (#,m,f)	Age (yrs)	Mean Weight (kg)	Conc. TCE - Inspired air (ppm)	Standard Deviation Inspired air (± ppm)	Exposure Duration	Time from beginning of exposure (hr)	Mean % TCE Retained	Absorbed TCE (mg)	Mean Conc. TCE - Expired Air after Exposure (ppm)	Conc. TCE in Aveolar Air (ppm)	Cumula-tive Conc. TCA in Urine (mg)	Cumula-tive Conc. total TCOH in Urine (mg)
						5.50				19.43		
						5.56				24.16		
						5.63				27.02		
						6.67				35.19		
						6.60				27.72		
						6.84				35.45		
						48.79					68.67	355.27
						73.15					106.37	383.39
						96.17					139.19	395.24
						121.20					159.26	398.49
						145.20					170.84	399.64
						169.56					181.47	400.66
						192.94					190.81	401.52
						217.49					197.20	401.61
						239.45					202.46	
						264.96					206.14	
						286.58					210.60	
						311.26					212.70	
						335.40					214.66	
						359.54					214.76	
						382.54					215.11	
						406.34					216.28	
						429.38					216.63	
						453.58					215.93	
						476.62					216.78	

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Fernandez, 1975

Fernandez, G et al. 1975, Arch. des Maladies Prof. de Med.du Travail. 36(7-8):397-407 Fig. 1												
Subject (#,m,f)	Age (yrs)	Mean Weight (kg)	Conc. TCE - Inspired air (ppm)	Standard Deviation Inspired air (± ppm)	Exposure Duration	Time from beginning of exposure (hr)	Mean % TCE Retained	Absorbed TCE (mg)	Mean Conc. TCE - Expired Air after Exposure (ppm)	Conc. TCE in Aveolar Air (ppm)	Cumula-tive Conc. TCA in Urine (mg)	Cumula-tive Conc. total TCOH in Urine (mg)
Pe, m (Fig 1)	17	63	97	NA	8	0.05	72.80	992.00		17.48		
						0.15				27.48		
						0.34				29.17		
						0.81				24.26		
						1.42				36.03		
						2.06				32.64		
						2.90				25.00		
						5.05				20.08		
						5.07				21.16		
						5.28				26.77		
						6.49				27.77		
						6.61				26.18		
						6.71				25.16		
						25.49					15.36	340.72
						48.79					38.55	404.55
						73.15					54.51	414.70
						96.17					65.04	418.58
						121.20					77.38	419.60
						145.20					91.47	420.73
						169.56					98.01	421.14
						192.94					105.30	422.01
						217.49					110.25	
						239.45					117.40	
						264.96					121.24	
						286.58					121.59	

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Trichloroethylene Dosing Studies

Fernandez, 1975

Fernandez, G et al. 1975, Arch. des Maladies Prof. de Med.du Travail. 36(7-8):397-407 Fig. 1												
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE - Inspired air (ppm)**	**Standard Deviation Inspired air (± ppm)**	**Exposure Duration**	**Time from beginning of exposure (hr)**	**Mean % TCE Retained**	**Absorbed TCE (mg)**	**Mean Conc. TCE - Expired Air after Exposure (ppm)**	**Conc. TCE in Aveolar Air (ppm)**	**Cumula-tive Conc. TCA in Urine (mg)**	**Cumula-tive Conc. total TCOH in Urine (mg)**
						311.26					122.95	
						335.40					123.46	
						359.54					126.70	
						382.54					128.01	
						406.34					129.68	
						429.38					130.81	
						453.58					131.84	
						476.62					131.10	
Hu, m (Fig 1)	29	76	54	NA	8	1.91	78.00	572.00		11.18		
						1.97				12.11		
						2.06				13.20		
						2.45				13.34		
						2.56				11.15		
						2.66				12.39		
						2.75				14.40		
						3.18				11.19		
						4.28				9.36		
						4.40				11.27		
						4.50				13.34		
						4.61				10.28		
						5.77				10.15		
						5.77				10.13		
						5.82				11.04		
						5.92				11.11	4.61	31.09

Fernandez, G et al. 1975, Arch. des Maladies Prof. de Med.du Travail. 36(7-8):397-407 Fig. 1												
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE - Inspired air (ppm)**	**Standard Deviation Inspired air (± ppm)**	**Exposure Duration**	**Time from beginning of exposure (hr)**	**Mean % TCE Retained**	**Absorbed TCE (mg)**	**Mean Conc. TCE - Expired Air after Exposure (ppm)**	**Conc. TCE in Aveolar Air (ppm)**	**Cumula-tive Conc. TCA in Urine (mg)**	**Cumula-tive Conc. total TCOH in Urine (mg)**
						6.96				12.51		
						7.01				10.06		
						7.08				12.52		
						7.81				12.80		
						7.91				13.59		
						21.89					18.08	99.04
						46.66					58.94	154.45
						71.04					87.67	168.71
						94.32					105.07	171.66
						118.49					116.89	179.77
						142.90					130.38	181.24
						167.16					135.36	184.42
						191.57					139.64	184.16
						215.71					142.67	
						239.90					144.58	
						264.17					146.75	
						287.95					147.81	
						312.00					148.72	
						335.54					149.22	
						359.90					150.68	
						383.57					150.47	
Ca, m (Fig 1)	27	74	54	NA	8	0.18	74.40	536.00		12.61		
						0.31				11.65		
						0.36				13.05		

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Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Fernandez, 1975

Fernandez, G et al. 1975, Arch. des Maladies Prof. de Med.du Travail. 36(7-8):397-407 Fig. 1												
Subject (#,m,f)	Age (yrs)	Mean Weight (kg)	Conc. TCE - Inspired air (ppm)	Standard Deviation Inspired air (± ppm)	Exposure Duration	Time from beginning of exposure (hr)	Mean % TCE Retained	Absorbed TCE (mg)	Mean Conc. TCE - Expired Air after Exposure (ppm)	Conc. TCE in Aveolar Air (ppm)	Cumula-tive Conc. TCA in Urine (mg)	Cumula-tive Conc. total TCOH in Urine (mg)
						0.48				13.56		
						0.56				14.12		
						0.62				15.76		
						0.71				13.57		
						1.14				14.93		
						1.24				14.07		
						1.35				16.06		
						1.89				15.00		
						2.00				15.61		
						2.05				14.14		
						2.14				14.42		
						2.94				10.15		
						3.00				9.27		
						3.09				9.28		
						3.22				12.12		
						4.52				15.39		
						4.60				13.56		
						5.59				14.07		
						5.68				14.35		
						5.81				14.49		
						6.51				13.29	3.82	39.04
						6.58				12.50		
						7.86				17.66		
						7.91				15.99		
						21.89					15.48	92.61
						46.66					53.19	135.72

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Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Fernandez, 1975

Fernandez, G et al. 1975, Arch. des Maladies Prof. de Med.du Travail. 36(7-8):397-407 Fig. 1												
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE - Inspired air (ppm)**	**Standard Deviation Inspired air (± ppm)**	**Exposure Duration**	**Time from beginning of exposure (hr)**	**Mean % TCE Retained**	**Absorbed TCE (mg)**	**Mean Conc. TCE - Expired Air after Exposure (ppm)**	**Conc. TCE in Aveolar Air (ppm)**	**Cumula-tive Conc. TCA in Urine (mg)**	**Cumula-tive Conc. total TCOH in Urine (mg)**
						71.04					72.57	159.84
						94.32					89.18	166.55
						118.49					98.10	171.67
						142.90					107.81	175.51
						167.16					113.51	175.84
						191.57					117.48	176.10
						215.71					124.36	
						239.90					128.80	
						264.17					129.55	
						287.95					132.02	
						312.00					133.23	
						335.54					134.36	
						359.90					134.95	
						383.57					135.37	

Fernandez, J *et al. 1977, Brit J Ind Med (34)43-55, Fig. 2,3,4*								
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE Inspired air (ppm)**	**Exposure Duration**	**Time from beginning of exposure (hr)**	**Conc. TCE in Aveolar Air (ppm) Fig 2**	**Cum Conc. TCA in Urine (mg) Fig 4**	**Cum Conc. total TCOH in Urine (mg) Fig 3**
Sub #1, sex-NA	NA	NA	54.0	8.0	7.6		3.2	76.6
					23.0		NA	172.8
					46.7		100.7	255.4
					70.8		140.7	299.6
					95.2		169.3	311.7
					118.9		190.2	324.1
					143.2		206.4	329.3
					166.9		216.8	NA
					191.1		225.1	NA
Sub #2, sex-NA	NA	NA	54.0	8.0	7.6		5.6	54.3
					23.0		36.0	189.0
					46.7		113.7	289.5
					70.8		166.5	318.8
					95.2		201.3	324.6
					118.9		224.1	342.7
					143.2		249.6	346.1
					166.9		260.0	350.0
					191.1		269.0	NA
Sub #3, sex-NA	NA	NA	97.0	8.0	7.6		5.6	104.2
					23.0		30.0	253.3
					46.7		71.4	360.0
					70.8		110.9	390.6
					95.2		145.2	404.3
					118.9		163.7	406.6
					143.2		177.9	408.7
					166.9		187.5	408.2
					191.1		199.3	410.7
Sub #4, sex-NA	NA	NA	97.0	8.0	7.6		NA	95.2
					23.0		NA	348.7
					46.7		NA	411.4
					70.8		NA	417.0
					95.2		NA	424.2
					118.9		NA	426.5
					143.2		NA	428.8
					166.9		NA	428.5
					191.1		NA	427.1

Fernandez, J *et al. 1977, Brit J Ind Med (34)43-55, Fig. 2,3,4*								
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE Inspired air (ppm)**	**Exposure Duration**	**Time from beginning of exposure (hr)**	**Conc. TCE in Aveolar Air (ppm) Fig 2**	**Cum Conc. TCA in Urine (mg) Fig 4**	**Cum Conc. total TCOH in Urine (mg) Fig 3**
Sub #5, sex-NA	NA	NA	97.0	8.0	7.6		8.9	109.5
					23.0		25.4	285.9
					46.7		88.5	386.9
					70.8		123.8	424.5
					95.2		177.4	436.9
					118.9		193.4	446.2
					143.2		215.7	451.6
					166.9		232.5	457.2
					191.1		244.7	460.8
5 subjects, sex NA	NA	NA	160.0	8.0	8.3	13.6		
					8.6	8.0		
					8.9	7.1		
					9.1	4.8		
					9.4	3.2		
					10.8	1.9		
					21.7	0.6		
					21.7	0.6		
					22.1	0.6		
					24.7	0.6		
					25.2	0.4		
					56.7	0.2		
5 subjects, sex-NA	NA	NA	135.0	8.0	8.2	20.7		
					8.6	9.5		
					9.2	4.4		
					9.4	3.5		
					42.7	0.2		
5 subjects, sex-NA	NA	NA	97.0	8.0	8.3	21.6		
					8.3	19.0		
					8.3	16.7		
					8.3	15.1		
					8.3	14.2		
					8.5	6.6		
					8.8	6.6		
					8.9	6.1		
					9.1	3.8		

Fernandez, J *et al. 1977, Brit J Ind Med (34)43-55, Fig. 2,3,4*								
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE Inspired air (ppm)**	**Exposure Duration**	**Time from beginning of exposure (hr)**	**Conc. TCE in Aveolar Air (ppm) Fig 2**	**Cum Conc. TCA in Urine (mg) Fig 4**	**Cum Conc. total TCOH in Urine (mg) Fig 3**
					9.5	3.9		
					9.5	3.5		
					9.9	3.6		
					10.3	2.8		
					10.8	2.6		
					10.7	2.4		
					11.7	2.4		
					11.7	2.3		
					11.7	2.1		
					12.2	1.8		
					12.1	1.4		
					12.7	1.7		
					13.8	1.2		
					22.3	0.9		
					22.4	0.8		
					22.7	0.8		
					23.3	0.8		
					23.5	0.7		
					24.5	0.5		
					24.6	0.4		
					24.5	0.3		
					25.9	0.7		
					25.8	0.4		
					26.0	0.4		
					26.1	0.3		
					26.3	0.4		
					28.5	0.3		
					28.5	0.2		
					28.9	0.3		
					29.3	0.6		
					29.5	0.7		
					30.0	0.4		
					30.2	0.4		
					30.1	0.3		
					31.8	0.6		
					31.9	0.5		
					31.9	0.3		
					32.1	0.3		
					33.3	0.5		
					33.5	0.5		

Fernandez, J *et al. 1977, Brit J Ind Med (34)43-55, Fig. 2,3,4*								
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE Inspired air (ppm)**	**Exposure Duration**	**Time from beginning of exposure (hr)**	**Conc. TCE in Aveolar Air (ppm) Fig 2**	**Cum Conc. TCA in Urine (mg) Fig 4**	**Cum Conc. total TCOH in Urine (mg) Fig 3**
					36.0	0.3		
					36.2	0.3		
					37.2	0.2		
					37.5	0.3		
					37.3	0.2		
					38.3	0.4		
					38.5	0.3		
					38.3	0.2		
					40.8	0.3		
					41.0	0.3		
					41.8	0.3		
					42.0	0.3		
					42.6	0.3		
					43.0	0.3		
					43.8	0.2		
					43.9	0.3		
					45.0	0.3		
					46.1	0.3		
					46.1	0.3		
					47.1	0.3		
					47.1	0.3		
					49.5	0.3		
					49.8	0.2		
					52.0	0.2		
					53.8	0.2		
					54.0	0.2		
					57.2	0.2		
5 Subjects, sex-NA	NA	NA	56.0	8.0	8.3	12.4		
					8.6	8.7		
					8.7	5.6		
					9.2	5.8		
					8.9	4.6		
					9.5	4.5		
					9.3	4.1		
					23.9	0.3		
					24.3	0.7		
					24.5	0.4		
					25.1	0.6		
					25.4	0.6		

Fernandez, J *et al. 1977, Brit J Ind Med (34)43-55, Fig. 2,3,4*								
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE Inspired air (ppm)**	**Exposure Duration**	**Time from beginning of exposure (hr)**	**Conc. TCE in Aveolar Air (ppm) Fig 2**	**Cum Conc. TCA in Urine (mg) Fig 4**	**Cum Conc. total TCOH in Urine (mg) Fig 3**
					28.8	0.2		
					30.8	0.2		
					31.0	0.2		
					31.3	0.4		
					31.8	0.2		
					32.1	0.2		
					47.8	0.3		
5 Subjects, sex-NA	NA	NA	54.0	8.0	8.3	8.0		
					8.3	7.5		
					8.3	6.9		
					8.3	6.4		
					8.4	5.8		
					8.3	5.3		
					8.4	4.6		
					8.7	4.5		
					8.8	3.6		
					9.1	3.4		
					9.0	3.0		
					9.1	2.7		
					9.3	2.5		
					9.4	2.8		
					9.6	2.3		
					9.8	2.7		
					9.9	2.4		
					10.2	2.3		
					10.3	2.2		
					11.2	1.5		
					11.3	1.4		
					12.2	1.3		
					12.6	1.1		
					13.0	1.1		
					13.6	1.1		
					13.7	1.3		
					14.4	0.9		
					14.7	0.9		
					15.6	0.9		
					15.7	0.9		
					16.5	0.8		
					16.7	0.8		

Fernandez, J *et al. 1977, Brit J Ind Med (34)43-55, Fig. 2,3,4*								
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE Inspired air (ppm)**	**Exposure Duration**	**Time from beginning of exposure (hr)**	**Conc. TCE in Aveolar Air (ppm) Fig 2**	**Cum Conc. TCA in Urine (mg) Fig 4**	**Cum Conc. total TCOH in Urine (mg) Fig 3**
					17.6	0.7		
					17.8	0.6		
					19.5	0.5		
					19.7	0.6		
					20.6	0.5		
					20.6	0.4		
					21.1	0.5		
					21.5	0.5		
					21.7	0.5		
					21.9	0.5		
					22.2	0.5		
					22.4	0.5		
					22.4	0.4		
					22.6	0.5		
					23.4	0.4		
					25.2	0.5		
					25.3	0.3		
					27.7	0.2		
					28.2	0.3		
					28.3	0.4		
					28.7	0.3		
					28.9	0.2		
					29.2	0.2		
					30.3	0.2		
					30.3	0.2		
					30.4	0.3		
					30.4	0.3		
					30.9	0.4		
					31.7	0.2		
					44.8	0.3		
					48.0	0.2		
					49.4	0.2		
					55.3	0.2		
					55.6	0.2		
Note: Alveolar concentrations is reported as a concentration, but actually is								
C(alv)/C(insp) x 100, and therefore is a percent retained. Please see Fig. 2								

Hake, C. *et. al.* 1973, Med Coll Wis., NTIS #PB82-151713, NIOSH-00080951 Tbl. III									
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Daily Conc. TCE - Inspired air (ppm)**	**Exposure Duration**	**Time from beginning of first exposure (hr)**	**Mean Conc. TCA in Urine (mg/24 hr) Tbl III**	**Cum. Conc. TCA in Urine (mg)**	**Mean Conc. total TCOH in Urine (mg/24 hr) Tbl III**	**Cum. Conc. total TCOH in Urine (mg)**
4 females	NA	NA	100	7.5 hr/d, 5 days	24	28	28	211	211
					48	81	109	291	502
					72	184	293	341	843
					96	225	518	294	1137
					120	241	759	296	1433
3 females	NA	NA	100	3 hr/d, 5 days	24	24	24	118	118
					48	36	60	102	220
					72	64	124	134	354
					96	74	198	99	453
					120	84	282	113	566
3 females	NA	NA	100	1 hr/d, 5 days	24	25	25	39	39
					48	23	48	64	103
					72	26	74	156	259
					96	22	96	51	310
					120	32	128	58	368
Notes:									
Only data on females were used from this study, most males imbibed in light to heavy consumptions during several evenings during each wk of the study.									

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Kimmerle, 1973

Kimmerle G & Eben A 1973. Arch Toxikol. 30, 127-38													
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE - Inspired air (ppm)**	**Std Dev Inspired air (+ppm)**	**Exp Dur (hr)**	**Time from start of exposure (hr)**	**Mean Conc. TCE - Expired Air after Exposure (ppm) Fig.1or 3**	**Conc. TCE in Blood (mg/l) Tbl. 1**	**Conc total TCOH in Blood (mg/l) Tbl. 1**	**Conc. TCA in Urine (mg/# of hrs) Tbl.2**	**Cum TCA in Urine (mg)**	**Conc. TCOH in Urine (mg/# of hrs) Tbl.2**	**Cum TCOH in Urine (mg)**
A (f)	20 - 50	NA	40.00	7.00	4.00	4.00		0.20	0.71	1.32	1.32	12.05	12.05
						5.00		0.10	0.69	NA	NA	NA	NA
						6.00		0.08	0.61	NA	NA	NA	NA
						7.00		not det.	0.57	NA	NA	NA	NA
						8.00			0.60	0.33	1.65	3.60	15.64
						24.00			0.47	4.16	5.80	26.10	41.74
						32.00			not det.	NA	NA	NA	NA
						48.00			0.24	12.60	18.40	20.22	61.96
						72.00			0.20	13.93	32.34	13.14	75.10
						96.00			<0.123	8.47	40.81	6.52	81.62
						120.00				7.80	48.61	3.65	85.26
						192 (24 hr value)				2.32	NA	1.30	NA
B (f)	20 - 50	NA	44.00	4.00	4.00	4.00		0.48	1.64	0.29	0.29	8.82	8.82
						5.00		0.15	1.62				
						6.00		0.11	1.34				
						7.00		0.08	1.20				
						8.00			1.30	1.55	1.84	16.12	24.94
						24.00			0.53	5.19	7.03	19.28	44.22
						32.00			0.66				
						48.00			0.13	12.82	19.85	16.70	60.92
						72.00			0.10	11.85	31.70	8.00	68.92
						96.00			<0.009	6.71	38.41	1.98	70.90
						120.00				not det.		not det.	
						192 (24 hr value)				3.68		0.24	

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Kimmerle, 1973

Kimmerle G & Eben A 1973. Arch Toxikol. 30, 127-38													
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE - Inspired air (ppm)**	**Std Dev Inspired air (+ppm)**	**Exp Dur (hr)**	**Time from start of exposure (hr)**	**Mean Conc. TCE - Expired Air after Exposure (ppm) Fig.1or 3**	**Conc. TCE in Blood (mg/l) Tbl. 1**	**Conc total TCOH in Blood (mg/l) Tbl. 1**	**Conc. TCA in Urine (mg/# of hrs) Tbl.2**	**Cum TCA in Urine (mg)**	**Conc. TCOH in Urine (mg/# of hrs) Tbl.2**	**Cum TCOH in Urine (mg)**
C (f)		NA	44.00	4.00	4 hr	4.00		0.28	1.78	0.47	0.47	23.80	23.80
						5.00		0.22	1.71				
						6.00		0.11	1.47				
						7.00		0.08	1.32				
						8.00			1.55	0.87	1.33	4.91	28.70
						24.00			0.52	12.76	14.09	30.11	58.81
						32.00			0.54				
						48.00			0.11	16.14	30.24	26.78	85.59
						72.00			0.05	12.41	42.64	7.69	93.28
						96.00			<0.009	8.65	51.29	2.69	95.97
						120.00						not det.	
						192 (24 hr value)				1.52		0.27	
D (f)		NA	44.00	4.00	4 hr	4.00		0.26	1.49	1.27	1.27	14.85	14.85
						5.00		0.19	1.34				
						6.00		0.10	1.24				
						7.00		0.08	1.17				
						8.00			1.36	2.44	3.72	29.76	44.61
						24.00			0.70	14.72	18.44	37.67	82.28
						32.00			0.67				
						48.00			0.23	22.09	40.53	31.06	113.34
						72.00			0.13	17.40	57.93	13.44	126.78
						96.00			0.05	11.50	69.43	4.47	131.25
						120.00						not det.	

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Kimmerle, 1973

Kimmerle G & Eben A 1973. Arch Toxikol. 30, 127-38													
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE - Inspired air (ppm)**	**Std Dev Inspired air (+ppm)**	**Exp Dur (hr)**	**Time from start of exposure (hr)**	**Mean Conc. TCE - Expired Air after Exposure (ppm) Fig.1or 3**	**Conc. TCE in Blood (mg/l) Tbl. 1**	**Conc total TCOH in Blood (mg/l) Tbl. 1**	**Conc. TCA in Urine (mg/# of hrs) Tbl.2**	**Cum TCA in Urine (mg)**	**Conc. TCOH in Urine (mg/# of hrs) Tbl.2**	**Cum TCOH in Urine (mg)**
						192 (24 hr value)				not det.		not det.	
H (m)		NA	44.00	4.00	4 hr	4.00		0.25	1.32			11.72	11.72
						5.00		0.13	1.28				
						6.00		0.08	1.19				
						7.00		0.08	1.04				
						8.00			1.09	0.59	0.59	25.70	25.70
						24.00			0.55	4.09	4.67	55.44	81.13
						32.00			0.40				
						48.00			0.16	6.82	6.82	21.44	21.44
						72.00			0.10	6.57	13.39	6.89	28.33
						96.00			0.04	5.67	19.06	2.58	30.91
						120.00				not det.		not det.	
						192 (24 hr value)				2.11		0.23	
E (m)		NA	40.00	7.00	4 hr	4.00		0.32	0.78	0.43	0.43	6.26	6.26
						5.00		0.12	0.66				
						6.00		0.12	0.64				
						7.00		not det.	0.59				
						8.00			0.57	0.77	1.20	8.89	15.15
						24.00			0.44	5.37	6.57	14.04	29.19
						32.00			not det.				
						48.00			0.20	5.40	11.97	7.59	36.78
						72.00			0.14	11.27	23.24	5.76	42.54
						96.00			<0.110	9.54	32.78	2.01	44.55

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Kimmerle, 1973

Kimmerle G & Eben A 1973. Arch Toxikol. 30, 127-38													
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE - Inspired air (ppm)**	**Std Dev Inspired air (+ppm)**	**Exp Dur (hr)**	**Time from start of exposure (hr)**	**Mean Conc. TCE - Expired Air after Exposure (ppm) Fig.1or 3**	**Conc. TCE in Blood (mg/l) Tbl. 1**	**Conc total TCOH in Blood (mg/l) Tbl. 1**	**Conc. TCA in Urine (mg/# of hrs) Tbl.2**	**Cum TCA in Urine (mg)**	**Conc. TCOH in Urine (mg/# of hrs) Tbl.2**	**Cum TCOH in Urine (mg)**
						120.00				5.19	37.96	1.67	46.22
						192 (24 hr value)				1.28		1.13	
F (m)		NA	40.00	7.00	4 hr	4.00		0.25	0.81	0.21	0.21	12.88	12.88
						5.00		0.13	0.68				
						6.00		0.08	0.61				
						7.00		not det.	0.55				
						8.00			0.50	0.28	0.49	11.83	24.71
						24.00			0.24	4.33	4.82	33.37	58.08
						32.00			not det.				
						48.00			0.08	12.42	17.24	14.64	72.72
						72.00			<0.047	11.27	28.51	3.68	76.40
						96.00				9.54	38.05	1.34	77.74
						120.00				5.15	43.20	0.86	78.60
						192 (24 hr value)				2.70		0.30	
G (m)		NA	40.00	7.00	4 hr	4.00		0.27	0.94	0.46	0.46	15.05	15.05
						5.00		0.13	0.69				
						6.00		0.08	0.81				
						7.00		not det.	0.70				
						8.00			0.66	0.36	0.82	6.84	21.90
						24.00			0.34	7.60	8.42	40.89	62.79
						32.00			not det.				
						48.00			0.13	10.63	19.05	22.49	85.28
						72.00			0.09	8.36	27.41	8.02	93.30
						96.00				5.78	33.18	2.49	95.79
						120.00				6.31	39.49	1.39	97.18

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Kimmerle, 1973

Kimmerle G & Eben A 1973. Arch Toxikol. 30, 127-38													
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE - Inspired air (ppm)**	**Std Dev Inspired air (+ppm)**	**Exp Dur (hr)**	**Time from start of exposure (hr)**	**Mean Conc. TCE - Expired Air after Exposure (ppm) Fig.1or 3**	**Conc. TCE in Blood (mg/l) Tbl. 1**	**Conc total TCOH in Blood (mg/l) Tbl. 1**	**Conc. TCA in Urine (mg/# of hrs) Tbl.2**	**Cum TCA in Urine (mg)**	**Conc. TCOH in Urine (mg/# of hrs) Tbl.2**	**Cum TCOH in Urine (mg)**
						192 (24 hr value)				3.61		0.32	
4 females	20-50	NA	40.00	7.00	4.00	4.00	3.62						
						4.50	1.53						
						5.00	0.95						
						5.50	0.69						
						6.00	0.59						
						6.50	0.42						
						7.00	0.33						
						7.50	0.28						
4 males	20-50	NA	40.00	7.00	4.00	4.00	3.34						
						4.50	1.89						
						5.00	1.21						
						5.50	0.79						
						6.00	0.68						
						6.50	0.57						
						7.00	0.47						
						7.50	0.37						
4 females		NA	48.00	3.00	y 5 days	4.00	3.15						
						4.50	1.26						
						5.00	0.53						
						5.50	0.34						
						6.00	0.29						

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Kimmerle, 1973

Kimmerle G & Eben A 1973. Arch Toxikol. 30, 127-38													
Subject (#,m,f)	Age (yrs)	Mean Weight (kg)	Conc. TCE - Inspired air (ppm)	Std Dev Inspired air (+ppm)	Exp Dur (hr)	Time from start of exposure (hr)	Mean Conc. TCE - Expired Air after Exposure (ppm) Fig.1or 3	Conc. TCE in Blood (mg/l) Tbl. 1	Conc total TCOH in Blood (mg/l) Tbl. 1	Conc. TCA in Urine (mg/# of hrs) Tbl.2	Cum TCA in Urine (mg)	Conc. TCOH in Urine (mg/# of hrs) Tbl.2	Cum TCOH in Urine (mg)
						6.50	0.22						
						7.00	0.23						
						96.00	2.81						
						98.00	0.48						
						99.00	0.38						
3 males & 1 female	20-30		48.00	3.00	4 hr/day 5 days								
J or I			48.00	3.00	y 5 days	0.00		0.00	0.00	0.00		0.00	
						4.00		0.42	2.05				
						5.00		0.13	1.67				
						8.00		0.09	1.60				
						9.00		0.00	1.41				
						10.00		0.00	1.26				
						24.00		0.00	1.17				
						28 (24 hr value)		0.51	2.00	4.18		46.14	
						33.00		0.17	1.80				
						48.00		0.00	0.92				
						52.00		0.41	2.38	14.99		75.46	
						57.00		0.00	1.72				

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Kimmerle, 1973

Kimmerle G & Eben A 1973. Arch Toxikol. 30, 127-38													
Subject (#,m,f)	Age (yrs)	Mean Weight (kg)	Conc. TCE - Inspired air (ppm)	Std Dev Inspired air (+ppm)	Exp Dur (hr)	Time from start of exposure (hr)	Mean Conc. TCE - Expired Air after Exposure (ppm) Fig.1or 3	Conc. TCE in Blood (mg/l) Tbl. 1	Conc total TCOH in Blood (mg/l) Tbl. 1	Conc. TCA in Urine (mg/# of hrs) Tbl.2	Cum TCA in Urine (mg)	Conc. TCOH in Urine (mg/# of hrs) Tbl.2	Cum TCOH in Urine (mg)
						72.00		0.00	0.95				
						76.00		0.51	2.58	27.56		53.95	
						81.00		0.00	2.06				
						96.00		0.00	1.27				
						100.00		0.85	2.51	26.10		62.62	
						104.00		0.00	2.14				
						105.00		0.00	2.12				
						120.00			2.11				
						124.00				51.47		120.09	
						144.00			0.51				
						148.00				29.04		20.29	
						168.00			0.27				
						172.00				14.95		17.78	
						192.00			0.14				
						196.00				not det.		not det.	
						216.00			0.08				
						220.00				not det.		not det.	
						240.00			0.05				
						244.00				not det.		not det.	
						264.00			0.03				
						268.00				not det.		not det.	
						388 (24 hr value)				1.37		0.20	
K			48.00	3.00	y 5 days	0.00		0.00	0.00	0.00		0.00	
						4.00		0.34	1.96				
						5.00		0.23	1.60				

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Kimmerle, 1973

Kimmerle G & Eben A 1973. Arch Toxikol. 30, 127-38													
Subject (#,m,f)	Age (yrs)	Mean Weight (kg)	Conc. TCE - Inspired air (ppm)	Std Dev Inspired air (+ppm)	Exp Dur (hr)	Time from start of exposure (hr)	Mean Conc. TCE - Expired Air after Exposure (ppm) Fig.1or 3	Conc. TCE in Blood (mg/l) Tbl. 1	Conc total TCOH in Blood (mg/l) Tbl. 1	Conc. TCA in Urine (mg/# of hrs) Tbl.2	Cum TCA in Urine (mg)	Conc. TCOH in Urine (mg/# of hrs) Tbl.2	Cum TCOH in Urine (mg)
						8.00		0.13	1.37				
						9.00		0.00	1.20				
						10.00		0.00	1.15				
						24.00		0.00	1.04				
						28.00		0.34	1.82	6.61		88.46	
						33.00		0.00	1.67				
						48.00		0.00	0.81				
						52.00		0.48	2.01	18.79		126.08	
						57.00		0.00	1.87				
						72.00		0.00	0.59				
						76.00		0.27	2.32	46.99		121.18	
						81.00		0.00	1.91				
						96.00		0.00	0.85				
						100.00		0.78	2.51	63.98		117.65	
						104.00		0.00	2.02				
						105.00		0.00	2.02				
						120.00			1.01				
						124.00				89.66		104.52	
						144.00			0.39				
						148.00				42.62		42.61	
						168.00			0.10				
						172.00				32.52		37.66	
						192.00			not det.				
						196.00				24.47		5.11	
						216.00			0.04				
						220.00				17.92		3.83	
						240.00			traces				

Kimmerle G & Eben A 1973. Arch Toxikol. 30, 127-38													
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE - Inspired air (ppm)**	**Std Dev Inspired air (+ppm)**	**Exp Dur (hr)**	**Time from start of exposure (hr)**	**Mean Conc. TCE - Expired Air after Exposure (ppm) Fig.1or 3**	**Conc. TCE in Blood (mg/l) Tbl. 1**	**Conc total TCOH in Blood (mg/l) Tbl. 1**	**Conc. TCA in Urine (mg/# of hrs) Tbl.2**	**Cum TCA in Urine (mg)**	**Conc. TCOH in Urine (mg/# of hrs) Tbl.2**	**Cum TCOH in Urine (mg)**
						244.00				13.65		2.03	
						264.00			0.00				
						268.00				11.56		1.04	
						388 (24 hr value)				2.10		0.08	
L (sex-NA)			48.00	3.00	y 5 days	0.00		0.00	0.00				
						4.00		0.28	1.28				
						5.00		1.18	1.01				
						8.00		0.09	0.90				
						9.00		0.00	0.80				
						10.00		0.00	0.72				
						24.00		0.00	0.57				
						28.00		0.34	1.44	5.34		63.33	
						33.00		0.00	1.85				
						48.00		0.00	0.55				
						52.00		0.34	2.09	12.29		86.56	
						57.00		0.00	1.40				
						72.00		0.00	0.68				
						76.00		0.34	1.57	31.68		84.44	
						81.00		0.00	1.25				
						96.00		0.00	0.51				
						100.00		0.51	1.97	61.15		86.00	
						104.00		0.00	1.64				
						105.00		0.00	1.32				
						120.00			0.51				
						124.00				76.70		89.61	

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Kimmerle, 1973

Kimmerle G & Eben A 1973. Arch Toxikol. 30, 127-38													
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE - Inspired air (ppm)**	**Std Dev Inspired air (+ppm)**	**Exp Dur (hr)**	**Time from start of exposure (hr)**	**Mean Conc. TCE - Expired Air after Exposure (ppm) Fig.1or 3**	**Conc. TCE in Blood (mg/l) Tbl. 1**	**Conc total TCOH in Blood (mg/l) Tbl. 1**	**Conc. TCA in Urine (mg/# of hrs) Tbl.2**	**Cum TCA in Urine (mg)**	**Conc. TCOH in Urine (mg/# of hrs) Tbl.2**	**Cum TCOH in Urine (mg)**
						144.00			0.18				
						148.00				47.81		24.52	
						168.00			not det.				
						172.00				48.33		6.13	
						192.00			0.05				
						196.00				35.77		3.43	
						216.00			0.03				
						220.00				18.71		2.56	
						240.00			0.00				
						244.00				18.33		1.32	
						264.00			0.00				
						268.00				16.35		0.71	
						388 (24 hr value)				2.18		0.07	
M (sex-NA)			48.00	3.00	y 5 days	0.00		0.00	0.00	0.00		0.00	
						4.00		0.17	2.85				
						5.00		0.17	2.39				
						8.00		0.09	2.28				
						9.00		0.00	2.05				
						10.00		0.00	1.98				
						24.00		0.00	1.30				
						28.00		0.34	2.91	2.93		116.10	
						33.00		0.00	2.43				
						48.00		0.00	0.83				
						52.00		0.27	2.53	9.26		130.58	
						57.00		0.00	2.26				

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Kimmerle, 1973

Kimmerle G & Eben A 1973. Arch Toxikol. 30, 127-38													
Subject (#,m,f)	Age (yrs)	Mean Weight (kg)	Conc. TCE - Inspired air (ppm)	Std Dev Inspired air (+ppm)	Exp Dur (hr)	Time from start of exposure (hr)	Mean Conc. TCE - Expired Air after Exposure (ppm) Fig.1or 3	Conc. TCE in Blood (mg/l) Tbl. 1	Conc total TCOH in Blood (mg/l) Tbl. 1	Conc. TCA in Urine (mg/# of hrs) Tbl.2	Cum TCA in Urine (mg)	Conc. TCOH in Urine (mg/# of hrs) Tbl.2	Cum TCOH in Urine (mg)
						72.00		0.00	0.47				
						76.00		not det.	2.32	17.29		117.11	
						81.00		0.00	2.42				
						96.00		0.00	0.76				
						100.00		not det.	2.87	18.61		95.13	
						104.00		0.00	2.52				
						105.00		0.00	2.29				
						120.00			1.01				
						124.00				63.84		97.56	
						144.00			0.20				
						148.00				57.88		41.05	
						168.00			0.03				
						172.00				17.09		40.92	
						192.00			not det.				
						196.00				19.87		3.07	
						216.00			0.00				
						220.00				12.08		0.93	
						240.00			0.00				
						244.00				11.74		0.39	
						264.00			0.00				
						268.00				8.54		0.13	
						388 (24 hr value)				3.56		0.00	

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Monster, 1976

Monster, G., *et al.* 1976. Arch. Occup. Environ. Hlth (38)87-102														
Subject (#,m,f)	Age (yrs) Tbl 4	Mean Weight (kg) Tbl 4	Conc. TCE - Inspired air (ppm)	Exp Dur (hr)	Dose Estimate (mg) Tbl3	Time from beginning of exposure (hr)	Mean Conc. TCE - Expired Air after Exposure (ppm) Fig 3a	Mean Conc. TCOH - Expired Air after Exposure (ppm) Fig 5a	TCOH in blood (mg/l) Fig 4a	TCA Conc. in blood (mg/l) Fig 6a	Cum. % of TCA excreted/ 8 hr (%)	Cum. Conc. TCA in Urine (mg)	Cum. % of TCOH excreted/ 8 hr (%)	Cum. Conc. total TCOH in Urine (mg)
4 males	29.8	69.7	70	4	390	0					0	0	0	0
						4	188.69244	0.042585	0.00044	3.51				
						6	28.521588	0.0393598	0.00042	5.07			9.058	35.3262
						14							22.162	86.4318
						22					1.8	7.02	29.095	113.471
						24	2.0320725	0.0105762	9.1E-05	8.19				
						30							34.276	133.676
						38							36.799	143.516
						46					4.8	18.72	38.25	149.175
						48	0.5805921	0.0025742	3.4E-05	8.97				
						54							39.346	153.449
						62							40.55	158.145
						70					6.8	26.52	41.193	160.653
						72				8.58				
						144				5.07				
						216				2.73				
4 males	29.8	69.7	140	4	755	0								
						4		0.0591909	0.00064	3.775				
						6	51.983465	0.0571242	0.00072	6.04			7.306	55.1603
						14							20.381	153.877
						22					1.0	7.55	27.392	206.81

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Monster, 1976

Monster, G., *et al.* 1976. Arch. Occup. Environ. Hlth (38)87-102														
Subject (#,m,f)	Age (yrs) Tbl 4	Mean Weight (kg) Tbl 4	Conc. TCE - Inspired air (ppm)	Exp Dur (hr)	Dose Estimate (mg) Tbl3	Time from beginning of exposure (hr)	Mean Conc. TCE - Expired Air after Exposure (ppm) Fig 3a	Mean Conc. TCOH - Expired Air after Exposure (ppm) Fig 5a	TCOH in blood (mg/l) Fig 4a	TCA Conc. in blood (mg/l) Fig 6a	Cum. % of TCA excreted/ 8 hr (%)	Cum. Conc. TCA in Urine (mg)	Cum. % of TCOH excreted/ 8 hr (%)	Cum. Conc. total TCOH in Urine (mg)
						24	3.3719004	0.0184612	0.00025	11.325				
						30							32.229	243.329
						38							35.136	265.277
						46					3.2	24.16	36.616	276.451
						48	0.983471	0.004073	5.8E-05	12.835				
						54							37.613	283.978
						62							38.345	289.505
						70					5.6	42.28	38.693	292.132
						72	0.4214876		1.3E-05	11.325				
						144				7.55				
						216				4.53				

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Muller, 1972

Muller G *et al.* 1972, Arch Toxikol (29) 335-40 Fig 1-2											
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE - Inspired air (ppm)**	**Exposure Duration**	**Time from beginning of exposure (hr)**	**Conc. TCA in Plasma (mg/l) Fig 1**	**Conc. Free TCOH in Blood (mg/l) Fig 1**	**TCA excreted (24 hr specimens) (mg) Fig 2**	**Cum. Conc. TCA in Urine (mg)**	**Total TCOH excreted (24 hr specimens) (mg) Fig 2**	**Cum. Conc. Total TCOH in Urine (mg)**
5	NA	NA	50	6 hr/dy, 5 dy	7	5.687					
					9		0.018				
					13	14.154					
					16		1.705				
					17	17.725					
					20		1.329				
					24			18.44	18.44	100.807	100.807
					32	18.228					
					34		0.518				
					37	27.441					
					40		2.074				
					42	30.026					
					45		1.353				
					48			37.101	55.541	130.895	231.702
					55	28.783					
					57		0.612				
					62	37.621					
					65		2.198				
					66	38.848					
					69		1.499				
					72			65.365	120.906	141.519	373.221
					81	36.443					
					82		0.715				
					88	43.685					
					90		2.255				
					93	44.989					
					94		1.515				

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Muller, 1972

Muller G *et al.* 1972, Arch Toxikol (29) 335-40 Fig 1-2											
Subject (#,m,f)	Age (yrs)	Mean Weight (kg)	Conc. TCE - Inspired air (ppm)	Exposure Duration	Time from beginning of exposure (hr)	Conc. TCA in Plasma (mg/l) Fig 1	Conc. Free TCOH in Blood (mg/l) Fig 1	TCA excreted (24 hr specimens) (mg) Fig 2	Cum. Conc. TCA in Urine (mg)	Total TCOH excreted (24 hr specimens) (mg) Fig 2	Cum. Conc. Total TCOH in Urine (mg)
					96			72.999	193.905	146.009	519.23
					105	42.645					
					106		0.658				
					112	49.027					
					114		2.265				
					116	51.482					
					118		1.633				
					120			98.289	292.194	153.569	672.799
					132		0.677				
					132	49.608					
					144			84.648	376.842	33.747	706.546
					153		0.213				
					156	43.506					
					192			44.806	421.648	4.414	710.96
					212	29.45					
					217		0.08				
					240			24.398	446.046	2.89	713.85
					260	19.701					
					288			19.864	465.91		
					299	15.003					
					336			13.805	479.715		
					356	11.531					
					408			5.568	485.283		
					429	5.994					

Muller G, *et al. 1974, Arch Toxicol (32)283-295, Fig. 1, 2, 3p.286*											
Subjects (#,m or f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE Inspired air (ppm)**	**Exposure Duration**	**Time from beginning of exposure (hr)**	**Conc. TCE in Aveolar Air (ppm) Fig 1**	**Avg. Conc. TCE in Blood (ug/ml) Fig 1**	**Avg. Conc. Total TCOH in Whole Blood (ug/ml) Fig 2a**	**Avg. Cum Conc. TCA in Urine (mg) Fig 2b**	**Avg. Conc TCA in plasma (mg/l) Fig 2a**	**Avg.Cum Conc. total TCOH in Urine (mg) Fig 2b**
5 m	20-30	NA	100	6.00	0.97	9.02	0.67	0.76		2.42	
					1.92	9.02	1.05	1.74		7.66	
					2.95	13.44	0.93	2.51		NA	
					3.97	14.27	0.83	3.43		11.88	
					5.00	18.34	1.02	4.18		NA	
					5.95	14.06	1.02	5.75		18.79	
					6.38	5.37	0.72	5.02		NA	
					6.53	3.94	0.52	4.47		NA	
					7.09	3.91	NA	4.47		NA	
					7.03	2.64	NA	4.84		NA	
					7.98	2.52	0.31	4.42		26.17	
					8.99	1.50	0.21	3.54		NA	
					10.00	0.76	0.18	3.59		28.59	
					12.01	0.37	0.13	3.03		35.35	
					14.07	0.37	0.11	2.61		38.23	
					24.55	0.19	0.07	1.24	43.215	46.65	244.774
					35.59	0.10	0.04	0.80		43.68	
					48.54	0.06	0.03	0.33	88.13	39.26	300.78
					59.51	0.06	0.02	0.24		37.44	
					72.00		NA	NA	133.53		315.90

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Muller, 1975

Muller *et al.* 1975, Arch Toxicol (33)173-189													
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE - Inspired air (ppm)**	**Exposure Duration**	**Time from beginning of exposure (hr)**	**Mean Conc. TCE - Expired Air after Exposure (ppm)**	**Conc. Free TCE in Blood (ug/ml)**	**TCOG in blood (ug/ml) Fig 7**	**Conc. free TCOH in Blood (ug/ml) Fig 1b**	**SEM of Total TCOH (ug/ml)**	**Total TCOH in blood (ug/ml)**	**Conc. TCA in Plasma (ug/ml) Fig 1a**	**SEM of TCA in Plasma**
males	20-26	62-77	50	6 hr/d, 5 d	6.432				0			5.629	
					13.752				1.69			14.23	
					17.664				1.312			17.585	
					24								
					31.56				0.432			18.327	
					38.592				2.057			27.672	
					42.864				1.306			30.398	
					48								
					55.992				0.599			28.781	
					62.88				2.173			37.704	
					66.504				1.493			39.144	
					72								
					81.504				0.712			36.45	
					87.864				2.237			43.839	
					91.608				1.503			45.069	
					92								
					105.96				0.64			42.906	
					111.624				2.246			49.181	
					115.368				1.615			51.712	
					120								
					130.56				0.656			49.746	
					144								
					153.984				0.185			43.644	
					192								
					209.832				0.069			29.567	

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Muller *et*						
Subject (#,m,f)	**TCA urinary excretion (mg/time)**	**Cumulative Conc. TCA in Urine (mg)**	**Standard Deviation TCA in Urine (+ mg/24 hrs)**	**Total TCOH urinary excretion (mg)**	**Cumulative Conc. total TCOH in Urine (mg)**	**Standard Deviation TCOH in Urine (+ mg/24 hrs)**
males		0			0	
	18.75	18.75	2.9825	101.899	101.899	13.0235
	37.98	56.73	4.2135	133.069	234.968	17.1825
	66.172	122.902	4.9605	143.975	378.943	7.055
	73.705	196.607	7.8065	149.511	528.454	22.2365
	99.253	295.86	6.967	156.983	685.437	17.59
	86.119	381.979	11.701	34.809	720.246	4.518
	45.375	427.354	4.3855	3.862	724.108	1.3635

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Muller, 1975

					240								
					257.64							19.647	
					288								
					296.808							14.739	
					336								
					354.36							11.426	
					408								
					428.688							5.89	
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE - Inspired air (ppm)**	**Exposure Duration**	**Time from beginning of exposure (hr)**	**Mean Conc. TCE - Expired Air after Exposure (ppm)**	**Conc. Free TCE in Blood (ug/ml) Fig 4**	**TCOG in blood (ug/ml) Fig 7**	**Conc. Free TCOH in blood (ug/ml)**	**SEM of Total TCOH (ug/ml)**	**Total TCOH in blood (ug/ml) Fig 7**	**Conc. TCA in Plasma (ug/ml) Fig 6a**	**SEM of TCA in Plasma**
males	20-26	62-77	100	6	1.025	6.555	0.804		0.999	0.0675			
					2.06	8.016						4.281	0.5
					3.024	9.934	1.019		2.397	0.196			
					4.045	10.702	1.38	0.689	3.348	0.2475	4.088	8.155	0.822
					5.035	13.444	1.112		3.657	0.2385			
					6.015	11.255	1.318	1.084	4.486	0.3525	5.666		
					6.168	6.558	0.957		4.539	0.3445		13.368	0.729
					6.329	5.298	0.744		4.481	0.3465			
					6.505	3.399	0.633		4.462	0.375			
					6.804		0.745		4.406	0.398			
					7.022	2.85	0.781		4.032	0.305			
					7.557	2.248	0.585		4.009	0.2865			
					8.004	2.233	0.44	0.88		0		17.852	1.5
					8.46								
					9.029	1.322	0.38		3.611	0.303			
					10.047	1.318	0.298		3.063	0.2325		19.607	0.805
					14.053	0.686	0.173		2.383	0.1835		21.491	1.0675
					24.077	0.566	0.065		1.057	0.09		28.998	0.805

	23.583	450.937	3.0255	2.255	726.363	1.4005
	19.663	470.6	2.843			
	13.403	484.003	2.4565			
	5.833	489.836	2.057			
Subject (#,m,f)	**TCA urinary excretion (mg/time) Fig 6**	**Cumulative Conc. TCA in Urine (mg)**	**Standard Deviation TCA in Urine (+ mg/24 hrs)**	**Urinary excretion of total TCOH (mg/hr)**	**Cumulative Conc. total TCOH in Urine (mg)**	**Standard Deviation TCOH in Urine (+ mg/24 hrs)**
males						
	0.251	0.251	0.1745	5.846	5.846	0.5365
				15.268	21.114	2.087
	0.917	1.168	0.2955			
				17.344	38.458	NA
	1.207	2.375	0.2965			
	1.943	4.318	NA	17.521	55.979	NA
	1.128	5.446	0.368	6.444	62.423	0.8725

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Nomiyama, 1971

Nomiyama K & Nomiyama H. 1971, Arch. Arbeitmed. (28):37-48, Fig 1,3b, 3c,5,															
Subject (#,m,f)	Age (yrs)	Mean Weight (kg)	Conc. TCE Inspired air (ppm)	Exp Dur (hr)	Time from beginning of exposure (hr)	Mean % TCE Retained	Std Dev TCE Retained (± %)	Mean Conc. TCE Expired Air after Exposure (ppm)	Std Dev TCE - Expired Air after Exposure (± ppm)	TCA in Urine (mg/12 hr)	Std Dev TCA in Urine (± mg/12 hrs)	Cum TCA in Urine (mg)	Conc. Total free TCOH & TCOG in Urine (mg/12 hr)	Std Dev total TCOH in Urine (± mg/12 hrs)	Cum Conc. Total TCOH in Urine (mg)
5 males	18-20	NA	250-380	2.67	2.67	34.6	7.3	56.18	14.14						
					3.231			19.17	2.90						
					3.971			16.37	2.42						
					4.67			11.71	1.68						
					5.67			7.83	1.09						
					6.67			6.61	0.77						
					7.67			4.71	0.58						
					14.67					7.51	5.50	7.51	115.67	52.37	115.67
					26.67					13.61	6.43	21.11	92.54	20.67	208.21
					38.67					31.97	17.09	53.08	60.67	19.12	268.88
					50.67					28.48	17.67	81.56	31.51	17.57	300.40
					62.67					30.23	24.71	111.78	16.69	11.76	317.09
					74.67					24.83	15.57	136.62	10.15	5.59	327.24
					86.67					22.31	14.13	158.93	6.21	3.80	333.44
					98.67					17.39	7.19	176.33	4.15	1.92	337.59
					110.67					13.94	6.85	190.27	3.31	2.31	340.90
					122.67					11.18	5.25	201.45	1.48	0.87	342.38
					134.67					8.01	4.77	209.46	2.43	1.53	344.81
					146.67					7.10	2.45	216.55	1.27	0.81	346.08
5 females	18-20	NA	250-380	2.67	2.67	37.8	3.8	42.31	6.60						
					3.231			14.60	2.11						
					3.971			13.24	2.84						

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Nomiyama, 1971

Nomiyama K & Nomiyama H. 1971, Arch. Arbeitmed. (28):37-48, Fig 1,3b, 3c,5,															
Subject (#,m,f)	Age (yrs)	Mean Weight (kg)	Conc. TCE Inspired air (ppm)	Exp Dur (hr)	Time from beginning of exposure (hr)	Mean % TCE Retained	Std Dev TCE Retained (± %)	Mean Conc. TCE Expired Air after Exposure (ppm)	Std Dev TCE - Expired Air after Exposure (± ppm)	TCA in Urine (mg/12 hr)	Std Dev TCA in Urine (± mg/12 hrs)	Cum TCA in Urine (mg)	Conc. Total free TCOH & TCOG in Urine (mg/12 hr)	Std Dev total TCOH in Urine (± mg/12 hrs)	Cum Conc. Total TCOH in Urine (mg)
					4.67			9.19	1.91						
					5.67			5.44	0.56						
					6.67			5.01	1.12						
					7.67			3.92	0.98						
					14.67					15.99	8.15	15.99	63.92	35.26	63.92
					26.67					39.81	23.70	55.80	74.22	37.36	138.15
					38.67					40.16	16.30	95.96	42.62	12.55	180.76
					50.67					41.16	16.25	137.12	33.68	11.08	214.44
					62.67					39.12	5.75	176.24	16.17	6.13	230.61
					74.67					27.49	6.52	203.73	13.57	3.28	244.19
					86.67					24.53	10.79	228.26	8.74	3.90	252.93
					98.67					18.50	8.68	246.76	4.77	2.37	257.69
					110.67					17.73	4.87	264.49	6.01	2.39	263.70
					122.67					10.74	1.85	275.23	2.96	0.84	266.66
					134.67					11.18	2.83	286.41	4.34	1.94	271.00
					146.67					6.73	0.83	293.14	2.42	1.02	273.42
Note: used Tanaka, 1968 approach for TCOH analysis, which was subtracting tca from total trichlo-cpds for tcoh															

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Nomiyama, 1979

Nomiyama H & Nomiyama K 1979, Ind Hlth (17)21-28 Fig. 1b, 1c												
Subject (#,m,f)	Age (yrs)	Mean Weight (kg)	Conc. TCE - Inspired air (ppm)	Exposure Duration	Mean Conc. TCE - Expired Air after Exposure (ppm)	Time from beginning of exposure (hr)	Urinary excretion of TCA (mg)	Cumulative Conc. TCA in Urine (mg)	Standard Deviation TCA in Urine (± mg/24 hrs)	Urinary excretion of total TCOH (mg)	Cumulative Conc. total TCOH in Urine (mg)	Standard Deviation TCOH in Urine (± mg/24 hrs)
5 m	NA	NA	250-380 (mean = 315)	2.7		12	8.043	8.043		114.125	114.125	
						24	14.021	22.064		89.27	203.395	
						36	32.779	54.843		57.735	261.13	
						48	27.242	82.085		30.959	292.089	
						60	31.595	113.68		17.122	309.211	
						72	26.464	140.144		9.849	319.06	
						84	22.599	162.743		5.944	325.004	
						96	16.844	179.587		4.228	329.232	
						108	14.034	193.621		3.348	332.58	
						120	10.75	204.371		1.516	334.096	
						132	7.88	212.251		2.354	336.45	
						144	6.764	219.015	111	1.247	337.697	111.1
Notes: TCOH analyzed using Tanaka et Ikeda, 1968, Brit. J Ind Med (25)214-219												

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Sato, 1977

Sato A, *et al. 1977. Brit J Indust Med. 34, 56-63*																	
Subject (#,m,f)	Age (yrs)	Mean Weight (kg)	Conc. TCE - Inspired air (ppm)	Exp Dur (hr)	Time from beginning of exposure (hr)	% Absorbed TCE expired	Mean Conc. TCE Expired Air after Exposure (mg/l)	Std Dev TCE - Expired Air after Exposure (±mg/l)	Conc. TCE in Blood (ug/ml) Fig 1	Std. Dev. TCE in Blood (± mg/24 hrs) Fig 1	Mean Conc. TCA in Urine (mg) Tbl 3	Std. Dev. TCA in Urine (± mg) Tbl 3	Cum. TCA in Urine (mg)	Mean Conc Total TCOH in Urine (mg) Tbl 3	Std. Dev. TCOH in Urine (± mg) Tbl 3	Cum. Total TCOH in Urine (mg)
4 males	20-21	61.6	100	4	0.00	20 - 30	0.256	0.051	1.823	NA	0	0	0	0	0	0
					0.05		0.041	0.01	1.018	NA						
					0.14				0.673	0.082						
					0.52		0.026	0.009	0.445	0.041						
					1.00		0.017	0.004	0.294	0.049	0.21	0.18	0.21	13.03	3.25	13.03
					1.51		0.013	0.001	0.221	0.04						
					2.00		0.01	0.003	0.179	0.026	0.25	0.08	0.46	11.00	4.66	24.03
					2.53		0.008	0.003								
					3.04		0.008	0.002	0.144	0.027						
					3.53		0.007	0.002								
					4.00		0.006	0.001	0.113	0.022	0.57	0.27	1.03	21.46	10.34	45.49
					4.49		0.006	0.002								
					5.00		0.006	0.002								
					5.98		0.005	0.002	0.078	0.014						
					6.99		0.004	0.001								
					8.00		0.003	0.001	0.051	0.012	2.37	1.57	3.4	36.28	5.55	81.77
					9.07		0.003	0.001								
					10.01		0.002	0	0.035	0.007						
					12.00						1.32	0.61	4.72	31.45	7.15	113.22
					16.00						0.93	0.26	5.65	26.70	7.64	139.92
					24.00						2.15	0.74	7.8	33.58	5.75	173.5
					36.00						4.32	1.31	12.12	39.70	10.99	213.2
					48.00						8.17	3.05	20.29	22.57	7.76	235.77
					60.00						7.79	1.84	28.08	17.03	3.76	252.8
					72.00						7.83	1.48	35.91	11.50	4.95	264.3

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Sato, 1977

Sato A, *et al. 1977. Brit J Indust Med. 34, 56-63*																
Subject (#,m,f)	Age (yrs)	Mean Weight (kg)	Conc. TCE - Inspired air (ppm)	Exp Dur (hr)	Time from beginning of exposure (hr)	% Absorbed TCE expired	Mean Conc. TCE Expired Air after Exposure (mg/l)	Std Dev TCE - Expired Air after Exposure (±mg/l)	Conc. TCE in Blood (ug/ml) Fig 1	Std. Dev. TCE in Blood (± mg/24 hrs) Fig 1	Mean Conc. TCA in Urine (mg) Tbl 3	Std. Dev. TCA in Urine (± mg) Tbl 3	Cum. TCA in Urine (mg)	Mean Conc Total TCOH in Urine (mg) Tbl 3	Std. Dev. TCOH in Urine (± mg) Tbl 3	Cum. Total TCOH in Urine (mg)
					84.00						6.95	2.64	42.86	6.52	4.62	270.82
					96.00						4.34	0.91	47.2	3.88	1.58	274.7
					108.00						4.56	1.22	51.76	6.00	1.39	280.7
					120.00						3.32	0.93	55.08	3.14	1.85	283.84
					132.00						3.23	1.18	58.31	2.17	1.29	286.01
					144.00						4.00	2.30	62.31	1.65	0.54	287.66
					156.00						2.44	0.32	64.75	0.88	0.70	288.54
					168.00						1.44	0.53	66.19	1.08	0.80	289.62
					180.00						2.55	0.32	68.74	1.17	0.53	290.79

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Stewart, 1970

Stewart RD, *et al.*		**1970. Arch Environ Health 20, 64-71**									
Experiment #	**Subject (#,m,f)**	**Conc. TCE Inspired air (ppm)**	**Exposure Duration (hr)**	**Time from beginning of exposure (hr)**	**Time from end of exposure (hr)**	**Mean Conc. TCE Expired Air after Exposure (ppm)**	**Mean Conc. TCE - Alveolar Breath during & after Exposure (ppm)**	**TCA in Urine (mg/24 hr)**	**Cum. TCA in urine (mg)**	**Conc. total TCOH in Urine (mg/24 hr)**	**Cum. total TCOH in urine (mg)**
1.0	5, sex-NA	200.0	7.0	26.6	19.6	3.6					
				31.0	24.0			31.0	31.0	147.0	147.0
				33.5	26.5	2.4					
				46.9	39.9	2.1					
				55.0	48.0			48.0	79.0	71.0	218.0
				70.2	63.2	1.1					
				79.0	72.0			33.0	112.0	94.0	312.0
				94.6	87.6	0.7					
2 thru 6	5-6, sex-NA	198.0	7/day, 5 days	0.0			0.0				
				3.0			76.0				
				3.5			10.3				
				7.5			10.8				
				8.0			8.3				
				10.0			5.1				
				13.0			3.3				
				24.0			1.2	51.0	51.0	308.0	308.0
				27.0			NA				
				27.5			10.9				
				31.5			11.2				
				32.0			9.4				
				34.0			4.4				
				37.0			2.8				
				48.0			1.6	175.0	226.0	359.0	667.0
				51.0			75.0				
				51.5			11.5				

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Stewart, 1970

Stewart RD, *et al.*		1970. Arch Environ Health 20, 64-71									
Experi-ment #	Subject (#,m,f)	Conc. TCE Inspired air (ppm)	Exposure Duration (hr)	Time from beginning of exposure (hr)	Time from end of exposure (hr)	Mean Conc. TCE Expired Air after Exposure (ppm)	Mean Conc. TCE - Alveolar Breath during & after Exposure (ppm)	TCA in Urine (mg/24 hr)	Cum. TCA in urine (mg)	Conc. total TCOH in Urine (mg/24 hr)	Cum. total TCOH in urine (mg)
				55.5			12.0				
				56.0			9.0				
				58.0			3.5				
				61.0			2.4				
				72.0			1.6	229.0	455.0	399.0	1066.0
				75.0			NA				
				75.5			8.4				
				79.5			8.7				
				80.0			7.7				
				82.0			3.5				
				83.0			2.9				
				96.0			1.6	306.0	761.0	538.0	1604.0
				99.0			NA				
				99.5			8.5				
				103.5			8.7				
				104.0			7.9				
				106.0			3.6				
				109.0			2.9				
				120.0				391.0	1152.0	405.0	2009.0
				136.0	16.2	3.5					
				144.0	24.0			255.0	1407.0	145.0	2154.0
				168.0	48.0			194.0	1601.0	149.0	2303.0
				184.0	64.0	1.2					
				192.0	72.0			114.0	1715.0	52.0	2355.0
				208.0	88.1	0.8					
				216.0	96.0			88.0	1803.0	40.0	2395.0

Stewart RD, *et al.*		1970. Arch Environ Health 20, 64-71									
Experi-ment #	Subject (#,m,f)	Conc. TCE Inspired air (ppm)	Exposure Duration (hr)	Time from beginning of exposure (hr)	Time from end of exposure (hr)	Mean Conc. TCE Expired Air after Exposure (ppm)	Mean Conc. TCE - Alveolar Breath during & after Exposure (ppm)	TCA in Urine (mg/24 hr)	Cum. TCA in urine (mg)	Conc. total TCOH in Urine (mg/24 hr)	Cum. total TCOH in urine (mg)
				240.0	120.0			50.0	1853.0	15.0	2410.0
				264.0	144.0			67.0	1920.0	4.0	2414.0
				336.0	216.0			29.0		14.0	
				408.0	288.0			8.0		14.0	
7.0	2, sex-NA	200.0	7.0	31.0	24.0			43.0	43.0	219.0	219.0
				55.0	48.0			62.0	105.0	143.0	362.0
				79.0	72.0			104.0	209.0	100.0	462.0
8.0	2, sex-NA	198.0	3.5	23.2	19.7	2.0					
				27.5	24.0			72.0	72.0	135.0	135.0
				30.2	26.7	1.5					
				51.5	48.0			63.0	135.0	57.0	192.0
				75.5	72.0			54.0	189.0	31.0	223.0
9.0	2 sex-NA	202.0	1.0	1.9	0.9	6.4					
				2.8	1.8	4.2					
				4.9	3.9	3.0					
				8.9	7.9	1.2					
				24.6	23.6	0.5					
				25.0	24.0			30.0	30.0	17.0	17.0
				39.0	38.0	0.3					
				49.0	48.0			45.0	75.0	0.0	17.0
				73.0	72.0			32.0	107.0	0.0	17.0

Stewart RD, *et al.*		**1970. Arch Environ Health 20, 64-71**									
Experiment #	**Subject (#,m,f)**	**Conc. TCE Inspired air (ppm)**	**Exposure Duration (hr)**	**Time from beginning of exposure (hr)**	**Time from end of exposure (hr)**	**Mean Conc. TCE Expired Air after Exposure (ppm)**	**Mean Conc. TCE - Alveolar Breath during & after Exposure (ppm)**	**TCA in Urine (mg/24 hr)**	**Cum. TCA in urine (mg)**	**Conc. total TCOH in Urine (mg/24 hr)**	**Cum. total TCOH in urine (mg)**
10, 1st exposure	2, sex-NA	100.0	4.0	4.4	0.4	7.7					
				4.8	0.8	5.9					
				5.5	1.5	4.9					
				9.1	5.1	3.4					
				12.9	8.9	2.3					
				23.6	19.6	1.1					
				28.0	24.0			69.0	69.0	163.0	163.0
				47.8	43.8	0.6					
				52.0	48.0			49.0	118.0	25.0	188.0
				76.0	72.0			66.0	184.0	4.0	192.0
10, repeat exposure				28.0	24.0			52.0	52.0	101.0	101.0
				52.0	48.0			57.0	109.0	13.0	114.0
				76.0	72.0			42.0	151.0	9.0	123.0

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Triebig, 1976

Triebig G, *et al. 1976, Zbl Bzkt Hyg, I Abt Orig B (163)383-416. Fig. 12,13,Tbl 3, Fig 17*										
Subject (#,m,f)	**Age (yrs)**	**Mean Weight (kg)**	**Conc. TCE - Inspired air (ppm)**	**Std Dev Inspired air (± ppm)**	**Exposure Duration**	**Time from beginning of exposure (hr)**	**Mean Conc. TCE - Expired Air after Exposure (ppm)**	**Median Conc. TCE in Blood (mg/l)**	**Median Conc. TCOH in Blood (mg/l)**	**Median Conc. TCA in Blood (mg/l)**
3 m & 4 f	NA	NA	135.6	15.1	6 hr/d, day#1	0	0-1	0.00	0.00	0.00
						6	12.3-31.9	1.31	6.20	12.14
			101	14.8	6 hr/d, day#2	24	1-4.6	1.11	3.83	32.81
						30	6.9-15.4	0.57	7.52	50.68
			104.1	16.9	6 hr/d, day#3	48	0-1	1.49	3.08	32.44
						54	6.2-15.4	1.23	7.70	51.31
			102	19.8	6 hr/d, day#4	72	0-1	2.05	3.16	51.29
						78	10.0-15.8	1.32	9.58	55.28
			99.8	15.8	6 hr/d, day#5	96	1.0-3.9	1.66	5.38	49.42
						102	8.5-13-9	1.38	9.79	65.22
						166	NA	0.91	0.58	28.92
Note: blood measurements taken at beginning and end of the 6 hr exposure each day, for 5 days.										
Last measurement made 64 hrs after end of exposures (at hour 166)										
6 Fig. 15, p. 403										
	NA	NA	135.6	15.1	6 hr/d, day#1	0			0.03	
						6			7.48	
			101	14.8	6 hr/d, day#2	24			3.69	
						30			7.35	
			104.1	16.9	6 hr/d, day#3	48			2.88	
						54			6.56	
			102	19.8	6 hr/d, day#4	72			2.47	
						78			6.84	
			99.8	15.8	6 hr/d, day#5	96			3.35	
						102			6.08	
f, sub.#	NA	NA	135.6	15.1	6 hr/d, day#1	0			0.08	
						6			4.02	
			101	14.8	6 hr/d, day#2	24			2.33	
						30			5.57	
			104.1	16.9	6 hr/d, day#3	48			2.43	
						54			5.69	
			102	19.8	6 hr/d, day#4	72			3.11	
						78			9.03	
			99.8	15.8	6 hr/d, day#5	96			5.54	
						102			9.01	
1f, sub #	NA	NA	135.6	15.1	6 hr/d, day#1	0			0.04	
						6			4.56	
			101	14.8	6 hr/d, day#2	24			4.09	
						30			8.10	
			104.1	16.9	6 hr/d, day#3	48			6.23	

Attachment I

Metabolites Data Over Time:
Trichloroethylene Dosing Studies

Triebig, 1976

Triebig G, *et al. 1976, Zbl Bzkt Hyg, I Abt Orig B (163)383-416. Fig. 12,13,Tbl 3, Fig 17*										
Subject (#,m,f)	Age (yrs)	Mean Weight (kg)	Conc. TCE - Inspired air (ppm)	Std Dev Inspired air (+ ppm)	Exposure Duration	Time from beginning of exposure (hr)	Mean Conc. TCE - Expired Air after Exposure (ppm)	Median Conc. TCE in Blood (mg/l)	Median Conc. TCOH in Blood (mg/l)	Median Conc. TCA in Blood (mg/l)
						54			11.82	
			102	19.8	6 hr/d, day#4	72			6.51	
						78			13.15	
			99.8	15.8	6 hr/d, day#5	96			5.52	
						102			9.95	
						166			1.48	
#7 Fig.	NA	NA	135.6	15.1	6 hr/d, day#1	0			0.04	
						6			6.04	
			101	14.8	6 hr/d, day#2	24			1.16	
						30			6.51	
			104.1	16.9	6 hr/d, day#3	48			3.21	
						54			7.59	
			102	19.8	6 hr/d, day#4	72			1.94	
						78			8.86	
			99.8	15.8	6 hr/d, day#5	96			2.17	
						102			7.70	
						166			0.13	
m, Sub #	NA	NA	135.6	15.1	6 hr/d, day#1	0			0.00	
						6			4.75	
			101	14.8	6 hr/d, day#2	24			1.21	
						30			3.42	
			104.1	16.9	6 hr/d, day#3	48			2.74	
						54			6.40	
			102	19.8	6 hr/d, day#4	72			5.18	
						78			10.75	
			99.8	15.8	6 hr/d, day#5	96			7.85	
						102			13.78	
						166			0.10	
m, Sub #	NA	NA	135.6	15.1	6 hr/d, day#1	0			0.00	
						6			6.01	
			101	14.8	6 hr/d, day#2	24			4.51	
						30			14.02	
			104.1	16.9	6 hr/d, day#3	48			5.01	
						54			13.00	
			102	19.8	6 hr/d, day#4	72			4.74	
						78			12.88	
			99.8	15.8	6 hr/d, day#5	96			5.27	
						102			12.02	
Note: Used Breimer *et al.* method.										

ATTACHMENT II

Metabolites Data Over Time:
Dichloroacetic Acid Dosing Studies

Curry SH, *et al. 1991. Biopharm. Drug Disposit, 12, 375-90 Fig. 1,2,3*					
Subjects	**Age (yr)**	**Weight (kg)**	**Dose (mg/kg)**	**Time from start of exposure (hr)**	**Conc DCA in plasma (mg/l)**
(1 volunteer), sex NA	18-45	within 10% of ideal	Crossover study-50 mg/kg (oral) Fig 1	0.1	11.6
				0.3	24.3
				0.6	75.1
				0.9	90.3
				1.1	115.5
				1.3	138.6
				1.6	140.1
				1.8	135.3
				2.1	137.8
				2.6	120.1
				3.1	114.1
				3.6	99.8
				4.1	106.1
				4.6	119.0
				5.0	80.6
				5.6	69.5
				6.1	64.7
				7.0	54.4
				8.0	50.9
				9.0	42.1
				10.0	41.7
				11.0	35.6
				12.0	31.9
same volunteer as above	18-45	within 10% of ideal	Crossover study-50 mg/kg (oral + vit. B1) Fig. 1	0.0	-0.3
				0.1	20.4
				0.2	47.6
				0.4	50.9
				0.5	55.6
				0.6	57.7
				0.8	71.1
				0.9	72.4
				1.0	94.0
				1.3	104.5
				1.5	127.2
				2.6	154.4
				3.1	158.2

Curry SH, *et al. 1991. Biopharm. Drug Disposit, 12, 375-90 Fig. 1,2,3*					
Subjects	**Age (yr)**	**Weight (kg)**	**Dose (mg/kg)**	**Time from start of exposure (hr)**	**Conc DCA in plasma (mg/l)**
				3.6	149.9
				4.1	148.0
				4.6	152.1
				5.1	150.9
				5.6	149.0
				6.1	143.0
				7.1	137.7
				8.0	146.1
				9.0	146.4
				10.0	127.3
same volunteer as above			Crossover study-50 mg/kg by IV Fig 1	5.1	148.4
				5.6	145.0
				6.1	147.6
				7.1	140.4
				8.1	147.3
				9.0	143.3
				10.0	136.5
				11.0	135.0
				12.0	135.8
				11.0	127.7
			(4 days between Crossover treatments)	12.0	128.3
1 male	18-45	within 10% of ideal	PK study-50 mg/kg (oral) Fig 2	0.0	0.3
				0.1	15.9
				0.2	41.1
				0.4	63.9
				0.5	74.9
				0.8	90.3
				0.9	70.7
				1.0	73.2
				1.3	97.3
				1.6	82.3
				1.8	73.8
				2.1	68.1
				2.6	59.9
				3.0	45.2
				3.5	37.0
				4.0	34.4
				4.6	43.3

Attachment II Metabolites Data Over Time: Dichloroacetic Acid Dosing Studies **Curry, 1991**

Curry SH, *et al. 1991. Biopharm. Drug Disposit, 12, 375-90 Fig. 1,2,3*					
Subjects	**Age (yr)**	**Weight (kg)**	**Dose (mg/kg)**	**Time from start of exposure (hr)**	**Conc DCA in plasma (mg/l)**
				5.0	22.6
				5.5	14.9
				6.0	7.8
				7.0	5.4
				8.0	6.7
				9.1	4.7
				10.0	6.1
				11.0	6.5
				12.0	3.4
1 female	18-45	within 10% of ideal	PK study-50 mg/kg (iv) Fig. 3	0.0	-0.1
				0.1	20.0
				0.3	84.5
				0.4	130.2
				0.5	170.7
				0.7	162.7
				0.8	165.5
				0.9	147.8
				1.0	134.7
				1.5	127.7
				2.0	114.3
				2.5	93.7
				3.5	47.0
				5.0	16.7
				6.0	5.4
				9.0	-0.1
4 males	18-45	within 10% of ideal	M/F study-assume 50 mg/kg by IV	0.2	47.2
				0.3	103.8
				0.4	152.8
				0.5	179.0
				0.8	155.1
				0.9	150.4
				1.0	146.3
				1.5	128.8
				2.0	119.4
				2.5	102.2
				3.5	83.2
				4.9	48.7
				5.9	31.5
				9.0	10.1
				10.0	7.6

Curry SH, *et al. 1991. Biopharm. Drug Disposit, 12, 375-90 Fig. 1,2,3*					
Subjects	**Age (yr)**	**Weight (kg)**	**Dose (mg/kg)**	**Time from start of exposure (hr)**	**Conc DCA in plasma (mg/l)**
				11.0	7.7
				12.0	6.8
4 females	18-45	within 10% of ideal	M/F study-assume 50 mg/kg by IV	0.0	-0.1
				0.1	38.4
				0.3	78.4
				0.4	112.6
				0.6	166.2
				0.8	146.9
				1.0	141.8
				1.2	136.0
				1.5	118.2
				2.0	103.4
				2.5	89.5
				3.5	63.2
				4.9	26.0
				5.9	10.1
				9.0	-0.5
				10.0	0.1
				11.0	0.3
				12.0	-0.6
1 female	18-45	within 10% of ideal	Multiple dose study-assume 50 mg/kg	2.0	158.4
				3.0	97.8
				4.0	49.4
				5.0	16.6
(same female as above)			Second dose (8 weeks)	3.0	105.8
				5.1	40.8
				6.2	17.0
				7.2	6.0
(same female as above)			Third dose (6 weeks)	2.1	133.2
				3.2	116.6
				4.0	78.2
				6.0	34.6
				7.0	24.9

Lukas G, *et al. 1980. J Pharmaceut Sci, 69(4) 419-21, Tbl IV*							
Subjects	**Age (yr)**	**Weight (kg)**	**Dose (mg/kg)**	**Time from start of 20 min. infusion of DCA (hr)**	**Conc DCA in plasma (mg/l)**	**Urinary excretion of DCA (mg)**	**Urinary excretion of total TCOH (mg)**
Subject 1	42	69.5	10	0.33	24.7		
				1	3.27		
				2	0.304		
				3	0.086		
				4	<0.04		
				6	<0.04		
				8	<0.04		
				10	<0.04		
				12	<0.04		
				24	<0.04		
				32	<0.04		
				48	<0.04		
Subject 2	38	69.1	10	0.33	19.9		
				1	4.44		
				2	0.585		
				3	0.117		
				4	<0.04		
				6	<0.04		
				8	sample lost		
				10	<0.04		
				12	<0.04		
				24	<0.04		
				32	<0.04		
				48	<0.04		
Subject 3	52	80.0	20	0.33	57.3		
				1	29.3		
				2	5.96		
				3	0.623		
				4	0.140		
				6	<0.04		
				8	<0.04		
				10	<0.04		
				12	<0.04		
				24	<0.04		
				32	<0.04		
				48	<0.04		

Lukas G, *et al. 1980. J Pharmaceut Sci, 69(4) 419-21, Tbl IV*							
Subjects	**Age (yr)**	**Weight (kg)**	**Dose (mg/kg)**	**Time from start of 20 min. infusion of DCA (hr)**	**Conc DCA in plasma (mg/l)**	**Urinary excretion of DCA (mg)**	**Urinary excretion of total TCOH (mg)**
Subject 4	26	83.3	20	0.33	74.9		
				1	46.8		
				2	11.2		
				3	4.68		
				4	0.608		
				6	0.175		
				8	<0.04		
				10	<0.04		
				12	<0.04		
				24	<0.04		
				32	<0.04		
				48	<0.04		

Wells, G. *et. al.* 1980. Diabetologia (19) 109-113. Fig. 4b					
Subjects	**Age (yr)**	**Weight (kg)**	**Dose (mg/kg)**	**Time from start of 30 min. infusion of DCA (hr)**	**Concentration DCA in plasma (mg/l) Fig. 4b**
1 subj. sex ?	Approximately 30	NA	35	0	0
				0.0	0.0
				0.5	117.0
				0.6	128.0
				0.6	117.0
				0.8	117.0
				1.0	119.0
				1.3	112.0
				1.7	89.0
				1.8	82.0
				2.0	64.0
				2.5	42.0
				2.9	25.0
				3.4	14.0
				3.9	7.0
				4.5	4.0
				5.0	2.0
				5.5	0.0

ATTACHMENT III

Metabolites Data Over Time:
Sodium Trichloroacetate Dosing Study

Attachment III Metabolites Data Over Time: Sodium Trichloroacetate Dosing Study **Muller, 1974**

Muller G, *et al. 1974, Arch. Toxicol. (32)283-295 Fig. 3b, 3a, 4a, 4b*						
Subjects	**Age**	**Dose of TCA Na (mg/kg)**	**Time from ingestion of TCA-Na (hr)**	**Conc TCA in plasma (ug/ml)**	**Urinary excretion of TCA (mg)**	**Urinary excretion of total TCOH (mg)**
3 m	20-30	3	0.4	22.9		
			0.9	29.5		
			2.9	23.0		
			5.6	24.1		
			10.0	21.8		
			23.7	17.2	41.7	ND
			33.6	15.7		
			48.7	14.2	15.7	ND
			58.7	11.5		
			71.9	8.9	14.8	ND
			82.2	8.4		
			95.9	5.4	12.4	ND
			106.2	5.8		
			120.0	5.0	9.1	ND
			147.7	3.4	7.0	
			168.0	2.5	3.7	
ND = not detected						

ATTACHMENT IV

Metabolites Data Over Time:
Trichloroethanol Dosing Studies

Marshall et al., 1954. Bull Johns Hopkins Hosp. (95): 1-18 Tbls VI, VIII							
Subject (#,m,f)	Age	Dose Chloral Hydrate Ingested (mg/kg)	Time from ingestion (hr)	Conc. TCA in plasma (mg/l)	Conc. total TCOH in plasma (mg/l)	Conc. Free TCOH in plasma (mg/l)	Cum. Percentage of dose excreted as urinary total TCOH (%)
M, 1, m	NA	15	0.25	NA	19	13	
			0.5				
			1				
			2	NA	9	5	7
			8				15
			24				26
O, 1, m	NA	15	0.25	NA	9	9	
			0.5				
			1	NA	13	14	
			2	NA	8	6	9
			8				18
			24				27
Ri, 1, m	NA	15	0.25	0	13	13	
			0.5	0	9	9	
			1	0	8	8	
			2				
			8				9
			24				18
S, 1, m	NA	15	0.25	0	6	6	
			0.5	0	14	15	
			1	0	7	7	
			2				8
			8				23
			24				40
Wo, 1, m	NA	15	0.25	2	NA	22	
			0.5	2	NA	13	
			1	2	NA	11	
			2	NA	NA	NA	8
			8	13	4	2	20
			24	18	5	0	36
			48	25		0	
			72	25			
Fi, 1, m	NA	15	0.25	0	NA	13	
			0.5	0	NA	11	
			1	0	NA	8	
			2				5
			8	3	5	4	19
			24	24	3	0	38
			48	18			

Muller G, *et al. 1974, Arch. Toxicol. (32)283-295 Fig. 3b, 3a, 4b, 4a*						
Subject (#,m,f)	**Age**	**Time from ingestion of 10 mg/kg TCOH (hr)**	**Conc. TCA in plasma (ug/ml)**	**Urinary excretion of TCA (mg)**	**Urinary excretion of total TCOH (mg)**	**Conc. total TCOH in blood (ug/ml)**
3 m	20-30	0.0	2.116			
		0.1	3.4			
		0.2	3.931			
		0.4	4.749			6.059
		0.5				5.018
		0.79				4.135
		1.429				3.839
		1.6	6.538			
		3.2	6.932			2.601
		5.8	11.467			1.968
		10.8	18.554			1.223
		23.4	24.531	25.975	83.721	0.504
		34.6	20.963			0.284
		47.7	17.349	40.529	16.162	0.164
		72.2	12.044	29.178	8.772	0.049
		95.5	9.234	24.095	3.44	0.02
		121.6	8.749	20.891	2.579	
		145.9	5.723	8.217		
		170.0	5.275	4.318		

Owens, A., *et. al.* 1955. Bull Johns Hopkins Hosp (97)320-326. Tbl III, IV										
Subject (#,m,f)	**Age**	**Weight**	**Daily Dose TCOH Ingested (mg/day)**	**Cum. Dose TCOH Ingested (mg/day)**	**Time from ingestion (hr)**	**Conc. TCA in plasma (mg/l)**	**Conc. urinary excretion of TCA (mg/day)**	**Cum. urinary excretion of TCA (mg)**	**Conc. urinary excretion of Total TCOH (mg/day)**	**Cum. urinary excretion of Total TCOH (mg)**
J.B.	NA	76.4	1000	1000	24	21	6	6	187	187
				2000	48	67	53	59	316	503
				3000	72	95	75	134	309	812
				4000	96	135	154	288	331	1143
				5000	120	140	265	553	312	1455
				6000	144	146	218	771	285	1740
				7000	168	159	312	1083	358	2098
				8000	192	160	287	1370	370	2468
				9000	216	169	398	1768	335	2803
				10000	240	171	334	2102	380	3183
				11000	264	187	412	2514	485	3668
				12000	288	187	340	2854	406	4074
				13000	312	187	390	3244	384	4458
				14000	336	187	354	3598	600	5058
I.H.	NA	80	1000	1000	24	13	5	5	365	365
				2000	48	34	13	18	370	735
				3000	72	52	34	52	315	1050
				4000	96	61	48	100	106	1156
				5000	120	60	43	143	32	1188
				6000	144	60	38	181	15	1203
				7000	168	60	42	223		1203
				8000	192	60	36	259	53	1256
Note: These doses are daily; time indicates the time from the initial dose										

ATTACHMENT V

Metabolites Data Over Time:
Chloral Hydrate Dosing Studies

Breimer, D. *et. al.* 1974, J of Chromatography, (88)55-63, Fig. 6								
Subject (#,m,f)	**Age**	**Weight**	**Dose Chloral Hydrate Ingested (mg/kg)**	**Time from ingestion (hr)**	**Conc TCA in blood (mg/l) Fig. 6**	**Conc total TCOH in blood (mg/l)**	**Conc Free TCOH in blood (mg/l) Fig.6**	**Conc TCOG in blood (mg/l) Fig.6**
				0.2			0.5	
				0.3			1.0	0.3
1 human, sex	NA	NA	15	0.4	0.2			
				0.5	0.5		1.8	0.9
				0.6	7.3		3.2	2.7
				1.0	8.6		5.2	2.5
				1.5			3.4	3.4
				1.9	7.2		2.6	3.3
				3.0			2.6	3.0
				5.0	12.3		2.1	2.5
				7.0	12.4		1.7	1.9
				9.0	15.5		1.3	1.6

Ertle T, *et al.* 1972, Arch Toxikol (29) 171-188, Fig. 5							
Subject (#,m,f)	**Age**	**Weight (kg)**	**Dose Chloral Hydrate Ingested (mg/kg)**	***Artificial time from end of exposures (hr)**	**Time from ingestion (hr)**	**Conc Total TCOH in blood (mg/l)**	**Values for time from start are derived by establishing peak times as 1 hr and altering other times accordingly. The higher TCOH levels for each time pair was assumed to be from the same volunteer.**
2,m	20-28	57-92	15	-0.199	0.6	4.671	
				-0.256	0.6	4.226	
				0.25	1.0	6.496	"maximum value is attained approx. 1h after ingestion" p.182
				0.312	1.0	7.379	"maximum value is attained approx. 1h after ingestion" p.182
				0.818	1.5	6.043	
				0.809	1.6	5.769	
				1.222	2.0	4.59	
				1.262	2.0	5.267	
				2.145	2.9	4.169	
				2.196	2.9	5.063	
				4.131	4.8	4.516	
				4.248	5.0	3.605	
				6.102	6.9	2.742	
				6.238	6.9	3.986	
				8.114	8.9	2.318	
				8.157	8.8	2.889	
				11.073	10.8	1.471	
				11.148	11.8	1.787	
				23.384	24.1	1.189	
				23.346	24.1	0.98	
				26.357	27.0	0.76	
				26.359	27.1	0.723	
				32.286	32.3	0.65	
				32.279	33.0	0.626	
				50.21	50.9	0.296	Used average of peak times to determine time from start.
				*Disregard this column; it serves only to assist in explanation of assumptions.			

Attachment V

Metabolites Data Over Time:
Chloral Hydrate Dosing Studies

Gorecki, 1990

Gorecki, D. *et. al. 1990, J Chromatography (528)333-341 Fig. 2*													
Subject (#,m,f)	Age	Weight (kg)	Dose Chloral Hydrate Ingested (mg)	Time from ingestion (hr)	Conc TCA in plasma (mg/l) Fig.2	Conc Free TCOH in plasma (mg/l) Fig.2	Conc TCOG in plasma (mg/l) Fig.2	Conc TCOG in urine (mg/12 hrs) Fig.3	Cum urinary excretion of TCOG (mg)	Conc urinary excretion of TCA (mg/12 hr) Fig.3	Cum urinary excretion of TCA (mg)	Conc urinary excretion of Free TCOH (mg/12 hr) Fig.3	Cum urinary excretion of free TCOH (mg)
1 male	NA	91	1000	0.6	2.5								
				0.7	12.3								
				1.1		9.3							
				2.0	14.1	8.6							
				2.2	15.2	6.0							
				3.0	14.5	4.7							
				3.9	16.0								
				4.5		4.0							
				5.3	19.9	3.4							
				7.1	21.7								
				8.7	21.4	2.5	0.1						
				13.5	28.3	2.1	0.1	238.7	238.7	14.5	14.5	4.1	4.1
				24.0	33.9	1.0	0.1	316.4	555.2	31.0	45.5	5.1	9.2
				38.2	37.8	0.6	0.0	358.1	913.3	51.5	97.0	5.2	14.4
				48.8	29.0			374.1	1287.4	71.0	168.1	5.0	19.4
				73.0	19.7			388.9	1676.3	132.1	300.2	5.1	24.4
				96.8	15.8			392.6	2068.9	167.2	467.3	5.3	29.8
				119.5	12.3			393.4	2462.2	180.9	648.3		
				143.0	7.7			393.3	2855.5	193.5	841.8		
				167.9	6.6			393.9	3249.4	203.1	1044.9		
				191.9	5.6			393.7	3643.1	208.4	1253.3		

Marshall et al., 1954. Bull Johns Hopkins Hosp. (95): 1-18 Fig 5, Tbl V							
Subject (#,m,f)	Age	Dose Chloral Hydrate Ingested (mg/kg)	Time from ingestion (hr)	Conc. TCA in plasma (mg/l)	Conc. total TCOH in plasma (mg/l)	Conc. Free TCOH in plasma (mg/l)	Cum % of dose excreted as urinary total TCOH (%)
Wa, 1 male	NA	16.5	0.25	19.02	NA	8.82	
			0.5	19.01	NA	7.85	
			1	18.95	NA	7.89	
			2				7
			8	57.74	3.72	3.69	17
			24	57.68	3.82	1.8	26
			48	55.42			
Bo, 1 male	NA	16.5	0.25	17.55		5.9	
			0.5	8.8		8.71	
			1	9.47		7.65	
			2				4
			8	17.55	4.95	2.84	18
			24	28.61	2.91	0.16	31
			48	31.64			
			72	31.62			
P, 1 male	NA	16.5	0.25	2	4	4	
			2	19	8	7	5
			8				16
			24				31
Mc, 1 male	NA	16.5	0.25	16	13	13	
			2	16	8	7	5
			8				14
			24				26
We, 1 male	NA	16.5	0.25	3		3	
			0.5	13		7	

Metabolites Data Over Time:
Chloral Hydrate Dosing Studies

Marshall et al., 1954. Bull Johns Hopkins Hosp. (95): 1-18 Fig 5, Tbl V							
Subject (#,m,f)	Age	Dose Chloral Hydrate Ingested (mg/kg)	Time from ingestion (hr)	Conc. TCA in plasma (mg/l)	Conc. total TCOH in plasma (mg/l)	Conc. Free TCOH in plasma (mg/l)	Cum % of dose excreted as urinary total TCOH (%)
			1	15		8	
			2				3
			8	43	2	4	9
			24	54	2	1	16
			48	52			
Fu, 1 male	NA	16.5	0.25	14		13	
			0.5	14		8	
			1	14		7	
			2				7
			8	19	3	2	23
			24	25	3	0	35
			48	27			
Ar, 1 male	NA	30	0.17	3.93		6.94	
			0.33	8.96		15.94	
			0.5	11.89		19.01	

Metabolites Data Over Time:
Chloral Hydrate Dosing Studies

Muller G, *et al. 1974, Arch Toxicol (32)283-295, Fig. 3a, 3b, 4a, 4b p. 288*							
Subject (#,m,f)	**Age**	**Conc. Ingested CH (mg/kg)**	**Time from ingestion of 15 mg/kg CH (hr)**	**Conc TCA in plasma (mg/l) Fig 3b**	**Conc total TCOH in blood (mg/l) Fig 3a**	**Urinary excretion of TCA (mg) Fig 4b**	**Urinary excretion of total TCOH (mg) Fig 4a**
3 males	20-30	15.0	0.4	5.6			
			0.5	8.1			
			0.5	13.5			
			0.5	16.3	6.9		
			1.4	17.1	5.3		
			1.6		4.3		
			3.0	19.7	3.6		
			5.7		2.4		
			10.3	29.5	1.4		
			24.4	34.1	0.7	53.6	157.7
			32.5	36.2	0.4		
			48.0	30.6	0.2	77.7	58.2
			72.0	20.5	0.1	67.4	20.1
			95.5	16.4	0.0	45.8	4.1
			120.0			27.7	2.7
			147.6	11.8		19.2	
			172.0	7.1		9.3	

Owens, A., *et. al.* 1955. Bull Johns Hopkins Hosp (97)320-326. Tbl I, II, Fig. 1										
Subject (#,m,f)	**Age**	**Weight (kg)**	**Daily Dose Chloral Hydrate Ingested (mg/day)**	**Cum Dose (mg)**	**Time from ingestion (hr)**	**Conc TCA in plasma (mg/l) Tbl I, II, Fig. 1**	**Conc urinary excretion of TCA (mg/day) Tbl I, II**	**Cum urinary excretion of TCA (mg)**	**Conc urinary excretion of Total TCOH (mg/day) Tbl I, II**	**Cum urinary excretion of Total TCOH (mg)**
C.B., sex?	NA	71.4	1000	1000	24	35	50	50	240	240
				2000	48	52	140	190	295	535
				3000	72	90	234	424	300	835
				4000	96	99	356	780	330	1165
				5000	120	101	362	1142	396	1561
				6000	144	101	337	1479	335	1896
				7000	168	104	415	1894	340	2236
				8000	192	106	445	2339	368	2604
				9000	216	112	460	2799	327	2931
				10000	240	120	433	3232	282	3213
				11000	264	120	548	3780	260	3473
				12000	288	119	670	4450	300	3773
				13000	312	120	439	4889	413	4186
				14000	336	120	608	5497	348	4534
G.B., sex?	NA	68	1000	1000	24	14	15	15	360	360
				2000	48	36	57	72	455	815
				3000	72	47	76	148	480	1295
				4000	96	53	67	215	357	1652
				5000	120	64	98	313	365	2017
				6000	144	74		313		2017
				7000	168	83	106	419	430	2447
				8000	192	85	130	549	430	2877
				9000	216	83	130	679	400	3277
				10000	240	83	107	786	570	3847
				11000	264	83	80	866	430	4277
				12000	288	85	122	988	260	4537
				13000	312	83	150	1138	348	4885
S.C., sex?	NA	140	1500	1500	0	0				
				2500	24	18.46				

Owens, A., *et. al.* 1955. Bull Johns Hopkins Hosp (97)320-326. Tbl I, II, Fig. 1										
Subject (#,m,f)	**Age**	**Weight (kg)**	**Daily Dose Chloral Hydrate Ingested (mg/day)**	**Cum Dose (mg)**	**Time from ingestion (hr)**	**Conc TCA in plasma (mg/l) Tbl I, II, Fig. 1**	**Conc urinary excretion of TCA (mg/day) Tbl I, II**	**Cum urinary excretion of TCA (mg)**	**Conc urinary excretion of Total TCOH (mg/day) Tbl I, II**	**Cum urinary excretion of Total TCOH (mg)**
				3500	48	50.33				
				4500	72	80.78				
				5500	96	58.38				
				6500	120	111.81				
				7500	144	109.04				
				8500	168	104.84				
				9500	192	99.09				
				10500	216	92.35				
				11500	240	83.71				
				12500	264	81.89				
				13500	288	82.03				
J.K. Sex?	NA	73	1500	1500	0	0				
				2500	24	19.96				
				3500	48	23.7				
				4500	72	38.19				
				5500	96	50.44				
				6500	120	65.69				
				7500	144	80.66				
				8500	168	77.45				
				9500	192	77.56				
				10500	216	80.76				
				11500	240	86.99				
				12500	264	91.33				
				13500	288	98.94				
				14500	312	104.46				
				15500	336	103.99				
				16500	360	107.81				
				17500	384	99.14				
Note: Daily Doses, time indicates hours from initial dose.										

Attachment V

Metabolites Data Over Time:
Chloral Hydrate Dosing Studies

Sellers, 1978a

Sellers EM, *et al. Clin Pharmacol Therapeut, 13(1) 37-49 Figs 1,2, Table I, p. 43*											
Subject (#,m,f)	**Age (yr)**	**Weight**	**Dose Chloral Hydrate Ingested (mg/kg)**	**Time from ingestion (hr)**	**Conc TCA in plasma (mg/l) Fig 1**	**Conc total TCOH in plasma (mg/l) Fig 1**	**Conc Free TCOH in plasma (mg/l)**	**Conc TCOG in plasma (mg/l) Fig 2**	**Cum. urinary excretion of TCOG (mg) Tbl I**	**Cum. urinary excretion of TCA (mg) Tbl I**	**Cum. urinary excretion of free TCOH (mg) Tbl I**
5 males	21-29	NA	15.0	0.5	5.4	7.6		2.0			
				1.0	7.5	8.4		3.4			
				1.5	8.1	8.1		2.2	19.6	2.9	3.9
				2.0	10.2	7.4		1.8			
				2.5	9.6	7.0		2.7			
				3.0					32.7	4.9	5.7
				3.5	10.0	6.4		1.2			
				4.5					46.9	6.0	7.2
				5.0	11.3	5.8		1.0			
				6.0					65.5	8.9	8.6
				6.5	13.0	5.4					
Note: The figure caption on Fig. 2 says concentrations of TCOG in plasma are given in ml/l of TCOH.											

Attachment V

Metabolites Data Over Time:
Chloral Hydrate Dosing Studies

Sellers, 1978b

Sellers EM, *et al. J. of Clin Pharmacol , Oct. 78, pp 457-461 Fig. 1*								
Subject (#,m,f)	**Age**	**Weight**	**Dose Chloral Hydrate Ingested (mg/kg)**	**Time from ingestion (hr)**	**Conc TCA in plasma (mg/l)**	**Conc total TCOH in plasma (mg/l)**	**Conc Free TCOH in plasma (mg/l)**	**Conc TCOG in plasma (mg/l)**
7 males	21-29	NA	15.0	0.5	5.3	9.6	7.7	1.9
				1.0	7.7	11.8	8.5	3.3
				1.5	9.2	10.2	8.1	2.1
				2.1	10.8	9.1	7.4	1.8
				2.5	9.7	9.5	6.8	2.7
				3.6	10.5	7.5	6.3	1.1
				5.0	11.9	6.7	5.7	1.0
				6.5	14.0	5.6	5.2	0.4
				24.0	35.9	2.3	2.1	0.2

ATTACHMENT VI

Human Physiological Parameters for Use in PBPK Modeling

MEASURED PHYSIOLOGICAL DATA - BLOOD FLOW RATES

						Blood Flows (fraction of QC)							
Author	**Citation**	**Subs (m, f)**	**Age (yrs)**	**Ethnicity**	**Body Wt(kg)**	**Fat (QF)**	**Slow Per(QS)**	**Rapid Per**	**Liver (QL)**	**Lung (QLung)**	**Kidney (QK)**	**Breathing Rate(QP)**	**Cardiac Output(QC)**
Cowles, Borgstedt, Gillies	1971. Anesthesiology. 35(5):523-526				70*	0.048m 0.067f	0.10m**$_d$ 0.06f**		0.24m 0.187f		0.197m$_a$ 0.175f$_a$		378$_a$
Smith and Kampine	Circulatory Physiology, 3rd ed. Williams & Wilkins, 114-222				70*		0.20**$_v$				0.20$_u$		300$_t$
							0.90**$_w$			0.01 to 0.02$_x$			
Mapleson	1963				70*	0.04m 0.056f	0.1-0.24m 0.06-0.14f		0.12m 0.09f		0.2m 0.18f		assumed 3l78
Bell et al.	1968						0.095m 0.057f		0.43m 0.33f		0.07m 0.066f		assumed 378
Brobeck.	1979						0.13m 0.077f		0.154m 0.12f	0.043m 0.034f	0.21m 0.19f		assumed 378
Ganong.	1979						0.129m 0.077f		0.166m 0.129f		0.21m 0.183f		assumed 378
Guyton.	1982						0.12m 0.074f		0.21m 0.167f	0.013m 0.011f	0.177m 0.157f		assumed 378
Williams and Leggett	1989. Clin Phys Physiol Meas 10(3):187-217					0.05m 0.085f	0.17m 0.12f		0.25m 0.27f	0.025m 0.025f	0.19m 0.17f		
Layton, DW	1993. Health Physics. 64(1):23-35											450males$_f$ 324 fem$_f$	
												390f$_g$	
Hinrichsen et al.	1993. Br J Clin Pharmacol. 35(5): 461 6	7 m 5 f	26.1 avg SD=0.6		66.7 avg SD=2.8								384±18$_{jj}$ 382±18$_{jj}$
													380±12$_{jj}$ 394.8±18$_{jj}$
													323±12$_{kk}$ 324±12$_{kk}$

MEASURED PHYSIOLOGICAL DATA - BLOOD FLOW RATES

						Blood Flows (fraction of QC)							
Author	Citation	Subs (m, f)	Age (yrs)	Ethnicity	Body Wt(kg)	Fat (QF)	Slow Per(QS)	Rapid Per	Liver (QL)	Lung (QLung)	Kidney (QK)	Breathing Rate(QP)	Cardiac Output(QC)
													323±12[kk] 329±12[kk]
Barlett et al.	1991. Amer Soc for Clin Nutr. 53:1112-16	86 m	20.2 avg (19-22)	cauc	81.5 SD=18.2								
		49 m	25.5 avg (23-30)	cauc	74.6 SD=11.9								
		48 f	17.5 avg (16-18)	cauc	62.4 SD=12.6								
		129 f	20.6 avg (19-22)	cauc	62.2 SD=10.7								
		108 f	25.9 avg (23-30)	cauc	68.7 SD=16.4								
D.S. Dittmer and R.M. Grebe	1958. Handbook of Respiration.	17 m	16-34							388.8 [aa]			
		17 f	16-34							298.2 [aa]			
		11 m	20-29							382.8 [bb]			
		50 f	adults							400.8 [cc]			
		10 m	adults							421.8[dd]			
Jackson, Pollock & Ward[ee]	1960. Medicine & Science in Sports and Exercise 12(3):175-182	249 f	31.44 avg SD-10.8		57.15 avg SD=7.59	avg 0.241 SD=0.072							
		82 f	29.94 avg SD=11.2		57.95 avg SD=6.97								
Reitz, Mendrala and Guengerich	1989. Toxicology and Applied Pharma 97:230 246				70								

MEASURED PHYSIOLOGICAL DATA - BLOOD FLOW RATES

						Blood Flows (fraction of QC)								
Author	Citation	Subs (m, f)	Age (yrs)	Ethnicity	Body Wt(kg)	Fat (QF)	Slow Per(QS)	Rapid Per	Liver (QL)	Lung (QLung)	Kidney (QK)	Breathing Rate(QP)	Cardiac Output(QC)
Caldicott et al.	1993. European Heart Journal 14:696-700	10 m 8 f	35-82[ff]										174-186[gg] 228-270[hh]
Heistad, Abboud	1974. Anesthesiology. 41(2):139-156						At rest: 60 l/hr**						
							Stren Ex: 1,200-1,800 l/hr**						
Mukherjee and Roche[ll]	1984. Human Biology 56(1):79-109	140 m	over 18 avg 33.76 SD=9.82	middle class	79.02 SD=12.62								
		135 f	over 18 avg33.47 SD=9.37		61.51 SD=10.98								
Jackson and Pollock[mm]	1976. Medicine and Science in Sports 8(3):196-203	95 m	avg 20.2 SD=1.6		74.6 SD=10.7								
		83 f	avg 20.2 SD=1.2		57.5 SD=7.4								
Jackson and Pollock[nn]	1978. Br J Nutr 40:497 504	308 m	avg 32.6 SD=10.8		avg 74.8 SD=11.8								
Pirpiris et al.	1993. American Journal of Hypertension 6:287-294				71.7								288±6 to 312±18

Breathing Rate Measurement							
Author	**Citation**	**Subject**	**Diagnosis**	**Sex**	**Age**	**Wt (kg)**	**Ventilation Rate (l/hr)**
Gilbert et al.	1972. J Applied Physiology. 33(2):252-254	1	N	M	20	73	427.2
		2	N	M	24	72	516
		3	N	M	26	98	528.6
		4	N	F	44	73	396
		5	N	F	34	60	288
		6	N	F	29	54	396
		7	A	F	62	57	249
		8	A	M	48	67	562.2
		9	CF	F	18	44	654
		10	FA	M	69	51	398.4
		11	GB	M	28		666
		12	COAD	M	61	60	876
		13	COAD	M	63	76	600
		14	COAD	M	54	94	593.4
		15	N	M	23	93	567.6
		16	COAD	M	75	54	1122
		17	N	M	23	75	411.6
		18	N	M	23	62	370.2
		19	N	M	23	75	492
		20	N	F	64	86	351.6
		21	N	F	24	50	394.2
		22	N	F	21	42	364.2
		23	N	F	23	55	369
		24	N	F	23	56	439.8
		25	N	F	28	58	392.4
Notes:							
N=Normal							
A=Asthma							
CF=Cystic Fibrosis							
FA=Fibrosing Alveolitis							
GB=Guillain-Barre Disease							
COAD=Chronic Obstructive Airway Disease							
Subjects 1-14 were tested first by resting quietly in bed with the magnetometer electrodes in place while tidal volume was recorded continuously with a respirometer applied after 1 hr. Respirometer readings were not used.							
Subjects 6, 14, 15, 16 were studied with the same initial protocol plus after 1 hr, a noseclip was applied, but instead of the respirometer, only a very short mouthpiece open to room air was placed in the subject's mouth.							
Subject 1-6, 15 and 17-25 data were obtained for normal subjects breathing quietly unhindered by respiratory apparatus.							
Tidal volume and respiratory frequency were obtained as the average of at least 10 breaths for each set of data. Ventilation rate was calculated as the product of tidal volume and resp freq. Vent rate is expressed as BTPS.							
Tidal volume and resp freq are significantly higher with the apparatus on as opposed to off as shown by student t test for paired values.							

MEASURED PHYSIOLOGICAL DATA - ORGAN WEIGHTS											
						Volume (fraction BW)					
Author	Citation	Subs (m, f)	Age (yrs)	Ethnicity	Body Wt(kg)	Body Fat (VF)	Slow Perf(VS)	Rapid Perf	Liver (VL)	Lung	Kidney (VK)
Cowles, Borgstedt, Gillies	1971. Anesthesiology. 35(5):523-526				70*		0.43**$_d$			2.68 liters $_c$	0.004$_a$
Smith and Kampine	Circulatory Physiology, 3rd ed. Williams & Wilkins, 114-222				70*						0.0043
Williams and Leggett	1989. Clin Phys Physiol Meas 10(3):187-217	ref m, f	35		70 m 58 f						
Snyder et al.	1974. Report of the Task Group on Reference Man. ICRP #23. 40-328		assume 25, 20-30		70 male 58 female	0.19 m $_h$ 0.23 f $_h$	0.37 m $_i$ 0.31 f $_i$		0.026 m$_l$ 0.024 f$_l$	5.5 liters $_e$	0.004 m$_q$ 0.0047 f$_q$
					70.5 m $_o$ 57 f $_o$		0.40 m $_j$ 0.29 f $_j$		0.02 m$_m$ 0.025 f$_m$		0.004 m$_r$ 0.0046 f$_r$
					74 m $_p$ 58.5 f$_p$		0.31-0.51 m$_k$ 0.17-0.36 f$_k$		0.025 m$_n$ 0.025 f$_n$		
		ref man $_s$			70	0.214	0.4		0.026	0.014	0.0044
Barlett et al.	1991. Amer Soc for Clin Nutr. 53:1112-16	86 m	20.2 avg (19-22)	cauc	81.5 SD=18.2	0.191 SD=0.088					
		49 m	25.5 avg (23-30)	cauc	74.6 SD=11.9	0.167 SD=0.077					
		48 f	17.5 avg (16-18)	cauc	62.4 SD=12.6	0.265 SD=0.088					
		129 f	20.6 avg (19-22)	cauc	62.2 SD=10.7	0.259 SD=0.061					

MEASURED PHYSIOLOGICAL DATA - ORGAN WEIGHTS											
						Volume (fraction BW)					
Author	Citation	Subs (m, f)	Age (yrs)	Ethnicity	Body Wt(kg)	Body Fat (VF)	Slow Perf(VS)	Rapid Perf	Liver (VL)	Lung	Kidney (VK)
		108 f	25.9 avg (23-30)	cauc	68.7 SD=16.4	0.289 SD=0.096					
Jackson, Pollock & Ward [ee]	1960. Medicine & Science in Sports and Exercise 12(3):175-182	249 f	31.44 avg SD=10.8		57.15 avg SD=7.59	avg 0.241 SD=0.072					
		82 f	29.94 avg SD=11.2		57.95 avg SD=6.97	avg 0.248 SD=0.064					
Reitz, Mendrala and Guengerich	1989. Toxicology and Applied Pharma 97:230-246				70				0.031		
Caldicott et al.	1993. European Heart Journal 14:696-700	10 m 8 f	35-82 [ff]								
Mukherjee and Roche [ll]	1984. Human Biology 56(1):79-109	140 m	over 18 avg 33.76 SD=9.82	middle class	79.02 SD=12.62	0.197					
		135 f	over 18 avg33.47 SD=9.37		61.51 SD=10.98	0.284					
Jackson and Pollock [mm]	1976. Medicine and Science in Sports 8(3):196-203	95 m	avg 20.2 SD=1.6		74.6 SD=10.7	0.134					

MEASURED PHYSIOLOGICAL DATA - ORGAN WEIGHTS											
						Volume (fraction BW)					
Author	Citation	Subs (m, f)	Age (yrs)	Ethnicity	Body Wt(kg)	Body Fat (VF)	Slow Perf(VS)	Rapid Perf	Liver (VL)	Lung	Kidney (VK)
		83 f	avg 20.2 SD=1.2		57.5 SD=7.4	0.248					
Jackson and Pollock[nn]	1978. Br J Nutr 40:497-504	308 m	avg 32.6 SD=10.8		avg 74.8 SD=11.8	avg 0.177 SD=0.08					
Roche	1995. Asia Pacific J Clin Nutr 4:63-67	179 men[oo]	18-32	white		avg 0.149 SD=0.052					
		140 men[oo]	18-32	black		avg 0.106 SD=0.065					
		47 men[pp]	20-61	white		avg 0.186 SD=0.057					
		45 men[pp]	19-50	black		avg 0.197 SD=0.071					
		42 fem[pp]	20-57	white		avg 0.283 SD=0.066					
		45 fem[pp]	19-44	black		avg 0.289 SD=0.081					
Wang et al.[rr]	1994. Am J Clin Nutr 60:23-8	187 m	51 ±19	white	77± 11	0.193 ± 0.06					
		258 f	51 + 19	white	61 + 9	0.301 ± 0.087					

MEASURED PHYSIOLOGICAL DATA - ORGAN WEIGHTS											
						Volume (fraction BW)					
Author	Citation	Subs (m, f)	Age (yrs)	Ethnicity	Body Wt(kg)	Body Fat (VF)	Slow Perf(VS)	Rapid Perf	Liver (VL)	Lung	Kidney (VK)
		110 m	52 ± 18	asian	68 ± 10_{qq}	0.214 ± 0.063_{qq}					
		132 f	51 ± 17	asian	54 ± 8_{qq}	0.316 ± 0.065					
Ellis	1989. USDA/ARS Children's Nutrician Research Center. 385-400	175 m	20-24 25-29	white	79.9±14.2 71.7±9.3	19.8 kg ± 13 kg					
		1134 f	20-24 25-29	white	59.2±6.7 58.9±5.9	15.9 kg ± 3.4 kg					
Pirpiris et al.	1993. American Journal of Hypertension 6:287-294				71.7						
Wang et al.	1992. American Journal of Human Biology 4:501-510	99m 109f	51±20 50±17	asian	67±10 53±7	0.21-0.27	0.26-0.3				
		64m 48f	45±16 43±14	black	80±14 65±9	0.18-0.27	0.26-0.35				
		166m 212f	50±18 50±19	white	77±12 59±8	0.18-0.27	0.23-0.36				
Hinrichsen et al.	1993. Br J Clin Pharmacol. 35(5): 461-6	7 m 5 f	26.1 avg SD=0.6		66.7 avg SD=2.8						

* Default value from ICRP "standard man" and EPA 1988
** Assumed muscle
[a]Based on statistical analysis of 510 measurements by 45 investigators by Wade and Bishop.
[b]Kidney blood flow average of 169 determinations by four investigators reviewed by Wade and Bishop. (396 ml/100g/min, wt=300g)
[c]Lung air of 2,680 ml composed of the functional residual capacity (FRC) (2,430 ml) plus half of the tidal volume (250 ml). FRC is average of 86 values determined in studies of males in the supine position by five investigators, reviewed by Svanberg.
[d]Based on weighted average of 289 determinations by seven investigators: Tonnesen; Lassen, Lindbjerg and Munck; Lindbjerg; Higgendal and
[e]The lungs were distended to the dimensions of the internal thoraic cavity. The volume of the inflated lungs both before and after fixation was
[f]Roy and Courtay (1991)
[g]Gilbert et al. (1972). Mean ventilation rate of six females between 18 to 30 years and weighing an average of 52 kg. Derived from measurements
[h]Adapted from Moore et al. pg 162 using standard body weights. See Figures 31 and 32 in ICRP No. 23. (1974).
[i]Burger p. 2094. Data obtained by plotting data from several sources and drawing visually smoothed graphs.
[j]Male data from Anson p.92. adjusted weight for 70 kg adult male. Female data from Roessle and Roulet p.101. for ages 22-35 yrs. average 58 kg
[k]Ranges for adult males age 20-35 yrs from range of literature values. Female range of literature values for ages 22-35 yrs.
[l]Liver fraction for reference adult male and female (70 kg and 58 kg).
[m]Average liver volumes based on Boyd for 19-20 yr old males (31 samples) and females (26 samples) (70.5 kg and 57 kg respectively).
[n]Average liver volumes based on Boyd for 20-29 yr olf males (38 samples) and females (19 samples) (74 kg and 58.5 kg respectively).
[o]Average of data from Stoudt et al for ages 19-20. See Figure 5 from ICRP No.23.
[p]Average of data from Stoudt et al. for ages 20-29. See Figure 5 from ICRP No.23.
qAverage total volume of both kidneys for reference adult male and female.
[r]Average kidney volumes (both) for male (2,414 samples) and females (1,104 samples) age 20-40 yrs and 72kg/60kg respectively.
[s]Reference man from Table 105, pg 280 ICRP No. 23.(Snyder et al. 1974)
[t]Average healthy heart cardiac output. Pumping capacity can increase to 1,200 to 1,500 l/hr with modest increase of right atrial pressure and maximum sympathetic stimulation
[u]Of flow, only a modest portion is for metabolic needs, so the renal (A-V)O2 difference is relatively small. Greatest part of flow becomes glomerular filtrate and serves as the main regulator of the body's water and electrolyte balance.
[v]At rest.
[w]At maximal exercise diversion to the working muscles may be 90% of the cardiac output.

[x]The blood supply to the lung is only 1-2% of the left ventricular output (5 l/min).
[y]Twenty year study of normal, healthy volunteers from student population and surrounding community (age 6-86 years). Non-ethnic population. Body density determined by hydrodensitometry.
[z]Cavalieri measurements using magnetic resonance imaging of subject.
[aa]Baldwin et al. (1948) Medicine 27:243.
[bb]Robinson (1938) Arbeitsphysiologie 10:251.
[cc]Hurtado et al. (1934) Journal of Clinical Investigation 13:169.
[dd]Coster et al. (1958) Acta Med Scand. 162:47.
[ee]Sample used to derive generalized regression equations which were validated with a scond sample as recommended by Lord & Novick. Body fat estimated by skinfold thickness method.
[ff]All participants of study had an acute myocardial infarction complicated by left ventricular failure.
[gg]Baseline cardiac output of diseased heart prior to treatment. Cardiac output was estimated with suprasternal Doppler aortovelography which follows direct reading trends accurately.
[hh]Cardiac output after treatment with enoximone and dobutamine. See footnote [gg].
[ii]Study was completed on healthy individuals. Subjects were treated with placebo, nizatidine, and pirenzepine. Data recorded for cardiac outputs for placebo subjects only.
[jj]Cardiac output measured by impedance cardiography. Measurements were taken with patient in supine position and holding his or her breath at end-expiration.
[kk]Cardiac output measured by doppler ultrasound. Measurements were taken using dual-beam doppler echo-aortography.
[ll]Data gathered by hydrostatic weighing and anthropometry.
[mm]Approximately 15 percent were physical education majors or athletes. Anthropometric determinations and underwater weighing was used.
[nn]Ages range from 18-61 years of age. Body types ranged from athletic to heavy. Anthropometric measurements and hydrostatic weighing were used. Relationship between skinfold fat and body density was quadratic.
[oo]Vickery et al. Prediction of body density from skinfolds in black and white young men. Hum Biol 1988:57:261-71
[pp]Zillikens & Conway. Anthropometry in blacks: Applicability of generalized skinfold equations and differences in fat patterning between blacks and whites. Am J Clin Nutr 1990:52:45-51.
[qq]Significantly different from whites of same sex.
[rr]Measurements taken by anthropometry.

Attachment VI

Human Physiological Parameters
for Use in PBPK Modeling

Blood Flow Rates used in PBPK Models

PBPK MODELING PHYSIOLOGICAL DATA - (BLOOD FLOW)

					Blood Flows(fraction QC)							
Author	Citation	Subject (m, f)	Age (yrs)	Body Wt(kg)	Fat (QF)	Slow Per(QS)	Rapid Per(QR)	Liver (QL)	Lung (QLung)	Kidney (QK)	Breathing Rate(QP)	Cardiac Output(QC)
Allen B & Fisher J[1&2]	1992. Risk Anal. 13(1), 71-86	11 m' 12 m^2	27-34' 21-28^2	67-90' avg 71^2	0.05	0.25	0.44	0.26			12.9	15
Bois F, Zeise L & Tozer T	1990 Tox and Applied Pharma. 102, 300-315											
EPA Monte Carlo[6]	1986			70	0.05	0.07	0.26				alveolar 9	bld flow 11.4
Kerr et al.[6]	1976			55	0.02	0.11	0.31				alv 15.6	bld flow 16.2
Kawai et al.[3]	1994. Journal of Pharmacokinetics and Biopharm. 22(5),327-365			70*	0.051	0.14**		0.26 arterial	0.01	0.21		
Csanady et al.[7]	1994. Arch Toxicol. 68, 143-157			70	0.05	0.25	0.44	0.26			alveolar 300	372
Overton & Jarabek[4]	1989. Exp. Pathol. 37, 89-94			70*	0.05	0.19	0.52	0.24			alveolar 555.6	555.6
Chinery & Gleason[8]	1993. Risk Analysis. 13(1), 51-62			70	0.05	0.14	0.51	0.25			alveolar 348	348
International Life Sciences Institute[9&10]	1994. Physiological Parameter Values for PBPK Models. 1-103			males 70 females 58	0.05	0.19**		0.23		0.18	comment and [11]	312 (range 276-276)[20]
Knaak et al.[12]	1992. Tox and Applied Pharmacology. 120, 106-113			estimated 70								
Leung[13]	1992. Am. Ind. Hyg. Assoc. J. 53(6):369-374			70*	0.05 rest 0.06 lt wk	0.19 rest 0.51lt wk	0.51 rest 0.27 lt wk	0.25 rest 0.16 lt wk			av: 348 rest, 1320 lt work	348 rest 603 lt wk
Perbellini et al.[5]	1990. Am. Ind. Hyg. Assoc. J. 51(7):356-362			70*	0.04	0.16	0.50	0.30			alveolar 360-720	360-480

PBPK MODELING PHYSIOLOGICAL DATA - (BLOOD FLOW)

					Blood Flows(fraction QC)							
Author	Citation	Subject (m, f)	Age (yrs)	Body Wt(kg)	Fat (QF)	Slow Per(QS)	Rapid Per(QR)	Liver (QL)	Lung (QLung)	Kidney (QK)	Breathing Rate(QP)	Cardiac Output(QC)
Elizabeth A. Brown	AFIT/GEE/ENV/94S			70 m [a] 60 f [a]	0.08 m [b] 0.08 f [b]	0.29 m [b] 0.29 f [b]	0.38 m [b] 0.39 f [b]	0.25 m [b] 0.25 f [b]			450 m [a] 363 f [a]	336 m [b] 288 f [b]
Roy et al.[21]	1995. Risk Anal. 16(2): 147-160			70	0.05	0.16	0.26	0.25		0.25	348	348
Corley et al.[14]	1990. Toxicology and Applied Pharma. 103:512-527			70	0.05	0.19	0.26	0.25		0.25	347.9	347.9
Travis et al.[15]	1990. Tox & Applied Pharma. 102:400-420			70*	0.05	0.22**		0.25			300	372
Andersen et al.[16]	1987. Tox & Applied Pharma. 87:185-205			70*	0.05	0.19	0.52	0.24			348	348
Dankovic & Bailer[17]	1994. Fund & Applied Tox. 22:20-25	male		70* at rest	0.0288	0.2019	0.4616	0.3077			Alv Vent 420	312
		male		70* 50W exercise	0.0455	0.5435	0.2494	0.1616			Alv Vent 1,344	594
		male		70* light work	0.0400	0.4319	0.3188	0.2093			Alv Vent 1,042.2	501.6
		male		70* [d]	0.0500	0.1900	0.5200	0.2400			Alv Vent 348	348
Filser et al.	1993. IARC Scientific Publications No. 127:65-78.	male		70*	0.05	0.25**	0.44	0.26			Alv Vent 300	348[e]
Koizumi [f]	1989. Brit J of Ind Med. 46:239-249			70*	0.05	0.18	0.53	0.24			Alv Vent $13.607(bw)^{0.7}$	$17.636(bw)^{0.7}$
Fisher & Allen	1992. Risk Analysis 13(1):87-95				0.05	0.25	0.44	0.26			Alv Vent $12.6\ (bw)^{0.74}$	$14.9\ (bw)^{0.74}$
Clewell, Lee & Carpenter	1994. Risk Analysis 14(4):521-531			70	0.050	0.19	0.52	0.24			Alv Vent 347.9[g]	347.9[g]
Sato et al.[18]	1991. Brit J of Ind Med. 48:342-347				0.053 m 0.092 f	0.114 m ** 0.087 f**		0.069 m 0.069 f				$17.76(bw)^{0.7}$ m $16.02(bw)^{0.7}$ f
Tardif et al.	1995. Risk Analysis 15(3):335-342				0.05	0.25	0.44	0.26			18 $(bw)^{0.7}$	18 $(bw)^{0.7}$

PBPK MODELING PHYSIOLOGICAL DATA - (BLOOD FLOW)												
					Blood Flows(fraction QC)							
Author	Citation	Subject (m, f)	Age (yrs)	Body Wt(kg)	Fat (QF)	Slow Per(QS)	Rapid Per(QR)	Liver (QL)	Lung (QLung)	Kidney (QK)	Breathing Rate(QP)	Cardiac Output(QC)
Drozet al.	1989. Brit J of Ind Med. 46:447-460											
Luecke, Wosilait, Pearce & Young	1994. Teratology 49:90 103	mother		58								
Robinson, Balter & Schwartz	1992. Jour of Pharmacokinetics & Biopharm 20(6):591-609											
Andersen et al.	1991. Tox and Applied Pharma 108:14-27			83	0.05	0.19	0.52	0.24			Alv Vent 395	331
Davis and Mapleson	1981. Br J Anaesth 53:399-405		30-39	70*	0.053	0.177***		0.069		0.188		
Bernareggi and Rowland[19]	1991. Journal of Pharma and Biopharma 19(1):21-50			70*	0.045	0.129		0.283_h	0.898_i	0.1886		350****

PBPK MODELING PHYSIOLOGICAL DATA - ORGAN WEIGHTS

					Volume (fraction of BW)					
Author	Citation	Subject (m, f)	Age (yrs)	Body Wt(kg)	Body Fat (VF)	Slowly Perf(VS)	Rapid Perf(VR)	Liver (VL)	Lung	Kidney (VK)
Allen B & Fisher J[1&2]	1992. Risk Anal. 13(1), 71-86	11 m[1] 12 m[2]	27-34[1] 21-28[2]	67-90[1] avg 71[2]	0.19	0.62	0.05	0.026		
Bois F, Zeise L & Tozer T	1990. Tox and Applied Pharma. 102, 300-315									
EPA Monte Carlo[6]	1986			70	0.2	0.63	0.05			
Kerr et al.[6]	1976			55	0.15	0.63	0.1			
Kawai et al.[3]	1994. Journal of Pharmacokinetics and Biopharm. 22(5),327-365			70*	0.14	0.43**		0.02	0.017	0.004
Csanady et al.[7]	1994. Arch Toxicol. 68, 143-157			70	0.19	0.62	0.05	0.026		
Overton & Jarabek[4]	1989. Exp. Pathol. 37, 89-94			70*	0.23	0.62	0.04	0.03	0.01	
Chinery & Gleason[8]	1993. Risk Analysis. 13(1), 51-62			70	0.231	0.51	0.037	0.03		
International Life Sciences Institute[9&10]	1994. Physiological Parameter Values for PBPK Models. 1-103			males 70 females 58	0.2142	0.4**		0.03	0.008	0.004
Knaak et al.[12]	1992. Tox and Applied Pharmacology. 120, 106-113			estimated 70				mass 1.7 kg		
Leung[13]	1992. Am. Ind. Hyg. Assoc. J. 53(6):369-374			70*	0.16	0.41	0.04	0.02		
Perbellini et al.[5]	1990. Am. Ind. Hyg. Assoc. J. 51(7):356-362			70*	0.12	0.36	0.07	0.02	0.01 (residual capacity 0.024)	
Elizabeth A. Brown	AFIT/GEE/ENV/94S			70 m_a 60 f_a	0.2 m_a 0.3 f_a	0.64 m_c 0.55 f_c	0.06 m_c 0.05 f_c	0.026 m_a 0.023 f_a		

PBPK MODELING PHYSIOLOGICAL DATA - ORGAN WEIGHTS										
					Volume (fraction of BW)					
Author	Citation	Subject (m, f)	Age (yrs)	Body Wt(kg)	Body Fat (VF)	Slowly Perf(VS)	Rapid Perf(VR)	Liver (VL)	Lung	Kidney (VK)
Roy, Weisel, Lioy, Georgopoulos	1995. Risk Anal. 16(2): 147-160			70	0.23	0.51	0.033	0.031		0.0044
Corley et al.[14]	1990. Toxicology and Applied Pharma. 103:512-527			70	0.231	0.6105	0.0327	0.0314		0.0044
Travis et al.[15]	1990. Tox & Applied Pharma. 102:400-420			70*	0.19	0.58**		0.026		
Andersen et al.[16]	1987. Tox & Applied Pharma. 87:185-205			70*	0.231	0.621	0.0371	0.0314		
Dankovic & Bailer[17]	1994. Fund & Applied Tox. 22:20-25	male		70* at rest						
		male		70* 50W exercise						
		male		70* light work						
		male		70* [d]						
Filser et al.	1993. IARC Scientific Publications No. 127:65-78.	male		70*	0.19	0.62**	0.05	0.026	0.01	
Koizumi [f]	1989. Brit J of Ind Med. 46:239-249			70*	0.195	0.524	0.031	0.026		
Fisher & Allen	1992. Risk Analysis 13(1):87-95				0.19	0.62	0.05	0.026		
Clewell, Lee & Carpenter	1994. Risk Analysis 14(4):521-531			70	0.231	0.621	0.0371	0.0314	0.0115	

PBPK MODELING PHYSIOLOGICAL DATA - ORGAN WEIGHTS										
					Volume (fraction of BW)					
Author	Citation	Subject (m, f)	Age (yrs)	Body Wt(kg)	Body Fat (VF)	Slowly Perf(VS)	Rapid Perf(VR)	Liver (VL)	Lung	Kidney (VK)
Sato et al.[18]	1991. Brit J of Ind Med. 48:342-347				0.211 m 0.365 f	0.415 m ** 0.315 f **		0.023 m 0.023 f		
Tardif et al.	1995. Risk Analysis 15(3):335-342				0.19	0.62	0.05	0.026		
Droz et al.	1989. Brit J of Ind Med. 46:447-460								0.0091	0.0053
Luecke, Wosilait, Pearce & Young	1994. Teratology 49:90-103	mother		58	0.276	0.297**		0.024	0.0068	0.0047
Robinson, Balter & Schwartz	1992. Jour of Pharmacokinetics & Biopharm 20(6):591-609									
Andersen et al.	1991. Tox and Applied Pharma 108:14-27			83	0.23	0.62	0.0371	0.0314		
Davis and Mapleson	1981. Br J Anaesth 53:399-405		30-39	70*	0.196	0.524***		0.025	0.0066	0.0041
Bernareggi and Rowland[19]	1991. Journal of Pharma and Biopharma 19(1):21-50			70*	10 liters	30 liters**		1.69 liters	1.17 liters	0.31 liters

Footnotes
* default value from US EPA 1988 and ICRP "reference man"
** assumed muscle
***lean body mass
****assumed from other ref
[a]Snyder et al. (1975)
[b]Smith & Kampline (1990)
[c] Travis et al. (1990)
[d]Reitz et al. (1989).
[e]Schmidt&Thews 1977
[f]Ramsey & Andersen (1984)
[g]Based on 70 kg body weight and 15 l/hr for 1 kg animal using equation Alv Vent =15 l/hr $(bw)^{0.74}$
[h]Sum of hepatic artery plus portal vein flows.
[i]Total blood flow.
[1] Arms and Travis (1987). Volumes and flow rates come from this reference.
[2]Astrand et al. (1973). Ventilation rate and cardiac output comes from this reference.
[3]Bernareggi & Rowland
[3]Jansky & Hart
[3]Ichimura, Yokogawa & Yamana
[4]All values except alveolar ventilation and cardiac output are from Andersen et al. (1987). Alveolar ventilation rates were calculated by assuming that alveolar ventilation is 67% of minute volumes for humans (U.S. EPA, 1988).
[4]Minute volume used was recommended by the U.S. EPA default value for human ventilation, 20 m/day.
[5]Parameter References come from Eger 1974 and Mapelson 1973. Most of data addressed used an alveolar ventilation of 360 l/hr associated with a blood flow of 360 l/hr or a alveolar ventilation of 720 l/hr with a blood flow of 480 l/hr.
[6]Values for Rapidly perfused tissue group blood flow rate were computed at each simulation so that the sum of the blood flows was equal to 100% of the total flow.
[6]Values for the Poorly perfused tissue group blood volume parameter were computed at each simulation so that the sum of the volumes was equal to 90% of the blood volume.

[6]Volumes were determined by experimental data (S. Oie, University of California, personal communication). Body weight and flows were assumed using cumulative distribution function F(x) = (1-cos(3.14x))//2 ($0 \leq x \leq 1$) for 500 random samples.
[6]Body Weight was raised to the 0.74 power as a multiplier for the alveolar ventilation rate and total blood flow.
[6]The relationships used to scale parameters were assumed to be known with certainty. This assumption leads to an underestimate of the variance associated with the parameters of the model.
[6]Sensitivity analysis shows that uncertainty in the parameters, other than Vmax and Km, has a limited effect on the results. In the absence of suitable data, certain parameter distributions were based on the judgement of expert researchers.
[6]For blood flows and ventilation rates, an idealized symmetric distribution was used, which may not be realistic.
[7]Physiological parameters were taken from Armes and Travis (1988). Alveolar ventilation comes from Schmidt and Thews (1977).
[8]All parameters were the same as used by Corley et al. (1990).
[9]Values come from the International Committee on Radiation Protection (1975) Reference Man. Cardiac output values come from Astrand (1983). Arms and Travis (1988) report mean cardiac output values for unanesthetized humans range from 276 - 390 l/hr.
[9]Regional blood flows are a provisional measure of central tendency from Williams and Leggett (1989).
[10]See Williams and Legget. 1989 in Physiological Measurements worksheet.
[11]Based on values reported in ICRP (1975) and assumptions that dead space=$0.33V_T$ at rest and $0.2V_T$ during physical activity.
[11]Effects of exercise on respiratory analysis used Altman and Dittmer (1971) to adjust Balke (1969). Values for light to moderate work are consistent with Dankovic and Bailer (1994) in the recent reevaluation of Andersen et al. (1987).
[12]Study focused on the development of V_{max} and K_m values for metabolism of isofenphos by p-450 liver enzymes.
[13]U.S. EPA, Reference Physiological Parameters in Pharmacokinetic Modeling, A.D. Arms and C.C. Travis, (U.S. EPA 600/6-88/004), (1988).
[14]Organ volumes and blood flows were similar to those used by Andersen et al. (1987) or were taken from the literature (Caster et al., 1956; Davis and Mapleson, 1981; Gasiewicz et al., 1983).
[15]All values from Arms &Travis (1988)
[16]Taken from ICRP, 1975; Davis and Mapleson, 1981; Caster et al., 1956. Lung wt = 0.0115 * (body wt)$^{0.99}$
[17]At rest and 50 W exercise values from Astrand (1983), Table 3 & 4; Lt Work values from linear interpolation, assuming that "light work" corresponds to 33.67 W of exercise.
[18]Values for cardiac output for men were chosen assuming at rest for standard man (70kg). Cardiac output for women set at 10% lower than men. Values for men from Davis and Mapleson (1981).
[19]Organ volumes were taken from texbook of anatomy. Blood flows were from Guyton (Texbook of Medical Physiology).
[20]Cardiac Output: 312 l/hr at rest, 501.6 light work (33.67 W of exercise), 594 slightly more strenuous (50 W), 1800 strenuous exercise.
[21]Values from Corley et al.